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Scientists narrow down pool of potential height genes

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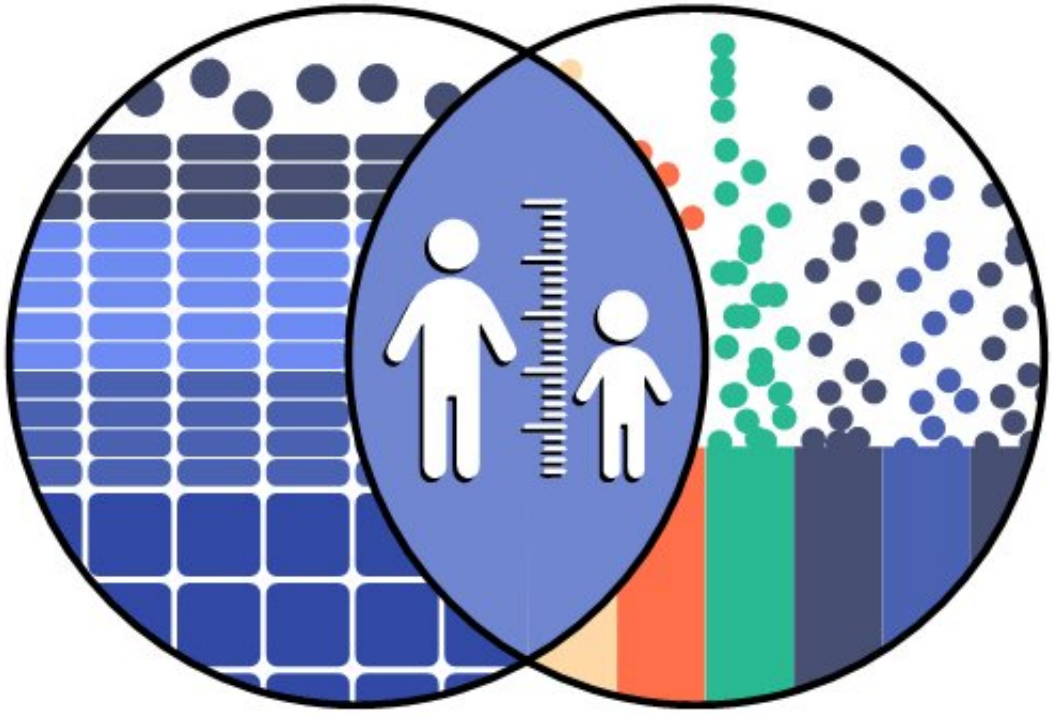

To better understand the genetics of height and skeletal growth, the study intersected two types of data—gene functions that alter chondrocyte proliferation and maturation in the growth plate (left illustration) and "hot spots" of heritability in human height from GWAS (right illustration). Credit: Nora Renthal

When it comes to height, our fate is sealed along with our growth plates—cartilage near the ends of bones that hardens as a child develops.

Research published April 14 in the journal *Cell Genomics* shows that cells in these plates determine the length and shape of our bones and can hint at our stature. The study identified potential "height genes" and found that genetic changes affecting cartilage cell maturation may strongly influence adult height.

"The study is really understanding the genetics of skeleton," says senior author Nora Renthal of Boston Children's Hospital and Harvard University. As a pediatric endocrinologist who cares for children with skeletal diseases, she is interested in understanding how bones grow. "Height is a good starting point to understand the relationship between genes, growth plates, and skeletal growth because we can measure the height of every human being."

To pinpoint height-associated genes, the team screened 600 million mouse cartilage cells to identify genes that, when deleted, can alter cell growth and maturation. These types of cellular changes in the growth plate are known to lead to variations in human height. The search turned up 145 genes mostly linked to skeletal disorders and are crucial for growth plate maturation and bone formation.

The team then compared the discovered genes with data from genome-wide association studies (GWAS) of human height. GWAS allows researchers to survey the entire human genome to identify hotspots where "height genes" are located in our DNA. But these regions can contain multiple genes, making it hard for researchers to track down and study an individual target.

"That's kind of like looking for your friend's house, but you only know the zip code," says Renthal. "It's difficult."

The comparison revealed that genes affecting cartilage cells overlap with hotspots from human height GWAS, precisely locating genes in our

DNA that likely play a role in determining our stature. Renthal and her team also discovered that many of the GWAS suggested height genes led to early maturation in cartilage cells. These findings suggest that genetic changes affecting cartilage cell maturation may influence height more.

Renthal notes that studies in mouse cells may not fully translate to humans, and GWAS are observational studies that cannot fully illustrate the cause and effects of height. But her study provides a novel method to bridge the two methods and provide new insights into human genetics.

Next, the team plans to use the method to understand hormones' effect on cartilage cells. They will also look into some of the 145 genes that have no known connection to skeletal growth. The investigation may reveal new genes and pathways that play a role in the bones.

"I see patients with skeletal dysplasia, where there isn't any treatment because genetics made their bones grow this way," says Renthal. "It's my hope that the more we can understand about the biology of the growth plate, the more we would be able to intervene at earlier times in growing skeletons and the life of a kid."

More information: Rodrigo Renthal, Genome-wide CRISPR Screening of Chondrocyte Maturation Newly Implicates Multiple Genes in Longitudinal Skeletal Growth and Height-GWAS Associated Loci, *Cell Genomics* (2023). DOI: 10.1016/j.xgen.2023.100299. www.cell.com/cell-genomics/ful … 2666-979X(23)00065-4

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