Researchers identify most powerful gene variant for height known to date

13 May 2020, by Jake Miller

Credit: CC0 Public Domain

A team of researchers from Harvard Medical School, Brigham and Women's Hospital, Socios En Salud, and the Broad Institute at Harvard and MIT report they have identified the single largest genetic contributor to height known to date.

The findings, published May 13 in *Nature*, are based on an analysis of samples from ethnically diverse Peruvians, a population known to have the shortest stature in the world.

The team identified a previously unknown, population-specific variant of the FBN1 gene (E1297G). The variant, found exclusively in individuals of Native American ancestry, showed a striking association with lower height.

Each copy of the gene was associated with an average of 2.2 centimeters (around 0.8 of an inch) reduction in height. People who have two copies, or two alleles, of the gene variant were, on average 4.4 centimeters (1.7 inches) shorter in stature. The effect is an order of magnitude greater than the effects that previously identified gene variants have on human height—in the range of 1 millimeter (0.04 inches).

"This study dramatically highlights the advantage of studying different populations and having a diverse, worldwide strategy to understanding the human genome," said study senior author Soumya Raychaudhuri, professor of medicine and of biomedical informatics at HMS, director for the Center for Data Sciences at Brigham and Women's Hospital, and an Institute member at the Broad Institute. "We learned new things about how complex genetic traits work. Our findings have implications for important diseases linked to FBN1 that we could not have learned without looking at this population."

The multi-institutional international research project brought together computational biologists, epidemiologists, community health workers, dermatologists and experts on a variety of genetic and infectious diseases, using a variety of genomic, computational and imaging techniques.

The results of their collaboration shed new light on the genetics of height, a key model system for studying complex, multigene systems that are crucial for understanding wellness and disease.

A wide range of mutations in the FBN1 gene has long been known to cause Marfan syndrome, an inherited connective tissue disorder marked by hypermobility of the joints, greater height compared to other family members and, in some instances, by cardiovascular problems.

The newly identified variant, however, is not associated with disease.

"One critical insight from this study is how genetic variants in the same gene can have very different effects," said lead author Samira Asgari, HMS research fellow in medicine at Brigham and Women's. "Before now, if you asked a geneticist what a variant in this gene would do, they would probably say that they cause a disease. But that's not what we found."

On the contrary, based on the researchers' analysis of the distribution of E1297G variant in the Peruvian population and throughout the wider Native American population, this variant may actually confer an evolutionary advantage, the researchers said, because it appears to have been selected for by evolution.

The study found that the new variant is notably more frequent in coastal Peruvian populations than in populations from the Andes or the Amazon, which suggests that short stature might be the result of adaptation to factors that are associated with the coastal environment in Peru, the researchers said.

These findings, based on one of the few studies of the genetics of Native American populations, highlight the importance of including diverse populations in biomedical research.

"It's really important to include underrepresented populations, particularly in these kinds of studies that are models for the way other multigene, complex traits function," said Megan Murray, the Ronda Stryker and William Johnston Professor of Global Health at HMS and a senior author of the study. "Leaving some people out means we might miss an important part of the picture we're trying to see. And any people who are left out aren't likely to reap the benefits of this kind of research."

Height is a complex genetic trait, and one that is easy to measure and provides an important model system for understanding how complex genetic systems work.

Meta analyses of genetic studies of height conducted on predominately European populations include more than 700,000 individuals, the researchers noted. This research has identified about 4,000 different genetic variations known to have an impact on an individual's height. Most such variants might make a person's stature less than one millimeter taller or shorter for each copy of the variant a person has.

"In comparison, this variant that we found has a 2.2 cm effect per allele," Asgari said. "That's huge for a height variant."

The new variant was not present in any of the large genetic studies conducted with European majority populations.

The genomes the team analyzed in Peru are quite distinct from those analyzed in Europe or North America. About 80 percent of the genes of an average Peruvian come from their Native American ancestry, according to previous research.

Until now, Peruvians have not been included in any genomic studies of height. by studying a small, previously overlooked population, the researchers pinpointed an allele that showed a bigger effect on height than all the other variants.

"Just amassing and amassing data isn't the answer," Raychaudhuri said. "If you're not looking at different populations, you're going to miss really important stuff."

The E1297G variant appears in the genomes of 5 percent in the Peruvian population, but it occurs in the genomes of less than 1 percent of people of Native American descent from Mexico. The variant is completely absent from the genome of people of European descent.

"We're doing studies in populations that are not normally on the map," Raychaudhuri said. "This relatively small project is the largest genetic study that's been done in Peru at this point."

The new study grew out of a series of projects led by HMS researchers in Peru, including a long-term collaboration between Murray and colleagues with the health care delivery nongovernmental organization Socios En Salud, the Peruvian affiliate of Partners In Health.

Murray's work in Peru has centered around the epidemiology and genetics of tuberculosis. Her collaboration with Raychaudhuri's team includes a previous study reported in *Nature Communications* last year that analyzed how a given individual's genetics impact their chances of becoming infected or ill with tuberculosis and identified a gene associated with TB progression.

After completing that project, Raychaudhuri and Asgari saw an opportunity to explore what the Peruvian genome might reveal about height. When their initial work revealed that there was a relationship to Marfan, other colleagues suggested they look for skin anomalies that are characteristic of variants in FBN1. The team grew, as they brought in Esther Freeman, HMS assistant professor of dermatology, a dermatologist and an epidemiologist at Massachusetts General Hospital. Working in Lima, the team tracked down homozygous individuals to analyze their skin, and found that it tracked with what would be expected with this genetic abnormality.

These diverse skills were all crucial to the process of discovery that allowed the researchers to produce this paper, the researchers said.

"If you want to do really cool science you have to get out of your corner and collaborate," Asgari said.

More information: A positively selected FBN1 missense variant reduces height in Peruvian individuals, *Nature* (2020). DOI: 10.1038/s41586-020-2302-0 , www.nature.com/articles/s41586-020-2302-0

Provided by Harvard Medical School