Height may be risk factor for varicose veins, study finds

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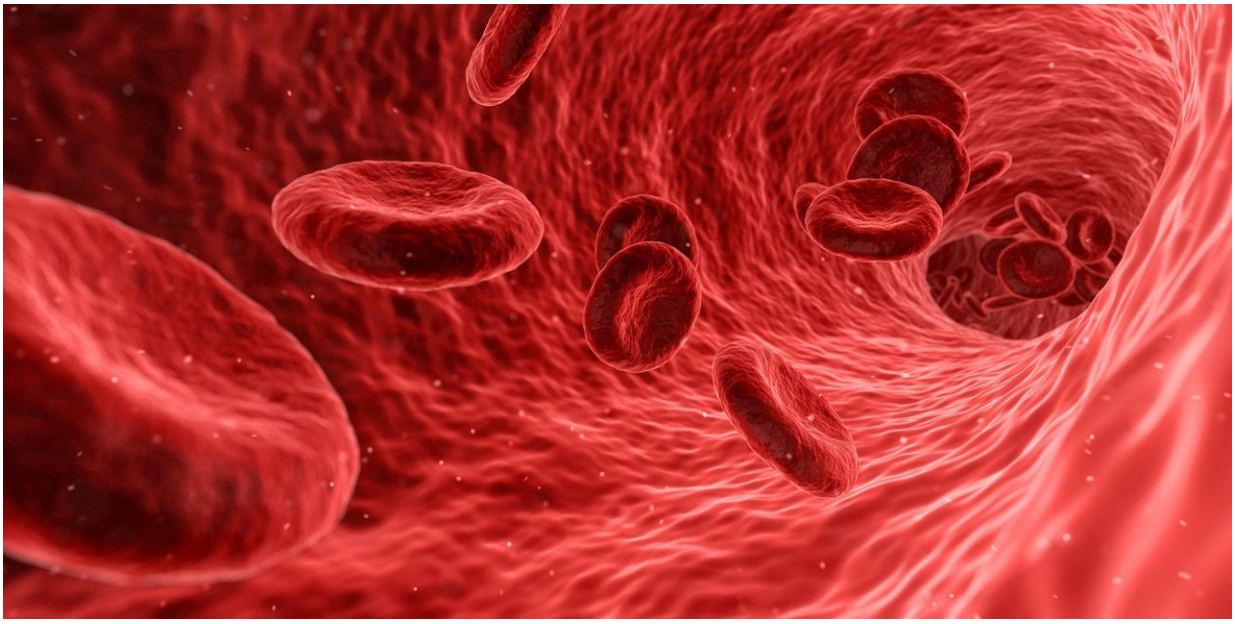

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The taller you are, the more likely you are to develop varicose veins, according to a study led by Stanford University School of Medicine researchers that examined the genes of more than 400,000 people in search of clues to what causes this common but little understood condition.

"Genes that predict a person's height may be at the root of this link

between height and varicose veins and may provide clues for treating the condition," said Nicholas Leeper, MD, associate professor of surgery and of cardiovascular medicine at Stanford.

The study also identified 30 genes linked to varicose vein disorder and to a strong genetic correlation with deep vein thrombosis. It will be published Sept. 24 in *Circulation*. Leeper and Erik Ingelsson, MD, Ph.D., professor of cardiovascular medicine, are the senior authors. Eri Fukaya, MD, Ph.D., clinical assistant professor of vascular surgery, and medical student Alyssa Flores share lead authorship.

Varicose veins are swollen, twisted veins that can be seen just under the surface of the skin, usually in the legs. More than 30 million people in the United States have varicose veins. Although the condition is often dismissed as nothing more than a cosmetic nuisance, it can cause moderate pain and has been linked to the more serious side effects of deep vein thrombosis, which occurs when a blood clot forms in one or more of the deep veins in the body.

'Shockingly little is known'

"The condition is incredibly prevalent but shockingly little is known about the biology," Flores said. "There are no medical therapies that can prevent it or reverse it once it's there." Treatment is mainly limited to surgical procedures, such as laser treatment or vein stripping. "We're hoping that with this new information, we can create new therapies, as our study highlights several genes that may represent new translational targets," she said.

Researchers used data from the UK Biobank—both a long-term study and genetic repository that includes genomic data on about a half-million people—to look for varicose vein risk factors using machine learning combined with epidemiological methods in 413,519 participants.

Further, they screened for genetic markers using genomewide association studies in 337,536 of the participants, 9,577 of whom had varicose vein disease. The study confirmed that currently established risk factors—including being older, female, overweight or pregnant, or having a history of deep vein thrombosis—are all associated with varicose veins.

"We confirmed that having had deep vein thrombosis in the past puts you at increased risk in the future," Leeper said. "Recent research suggests that the converse appears to be true as well. Having varicose veins puts you at risk of these blood clots."

The study also confirmed that surgery on the legs, family history, lack of movement, smoking and hormone therapy are risk factors. But the correlation they found between height and the condition was unexpected, the researchers said.

"We were very surprised to find that height came up from our machine-learning analyses," Flores said.

Turning the algorithm loose

Typically in a large, genetic study like this one, researchers use genomewide association studies to examine DNA variation that may be associated with an increased risk for a particular illness. Using this method, the researchers identified the 30 regions on the genome associated with varicose veins. But the researchers also used another method involving machine learning, a type of artificial intelligence, to cast a giant net to discover any previously unknown risk factors.

"These methods represent new ways of thinking about research," Ingelsson said. "You go in without a hypothesis about a specific biological mechanism and scan for something new. You could say that

you turn the machine loose on it. In this case, we included 2,716 predictors of varicose veins in this machine-learning algorithm. Then we let the algorithms find the strongest predictors of varicose veins."

In addition to height, the machine-learning algorithm showed that bioimpedance, a measure of how well the body impedes electric current flow, is a strong predictive marker for varicose veins. This measurement could potentially be used as a diagnostic tool to predict for varicose veins, Leeper said.

When height emerged from the machine-learning analysis as a possible risk factor, the researchers conducted further tests to see if it was an actual cause for the disease using mendelian randomization analyses, a statistical technique to determine causal effects.

"Our results strongly suggest height is a cause, not just a correlated factor, but an underlying mechanism leading to varicose veins," Ingelsson said.

He added, "By conducting the largest genetic study ever performed for varicose vein disease, we now have a much better understanding of the biology that is altered in people at risk for the disease."

More information: *Circulation* (2018). dx.doi.org/10.1161/CIRCULATIONAHA.118.035584

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