Novel gene identified as genetic cause of portal hypertension

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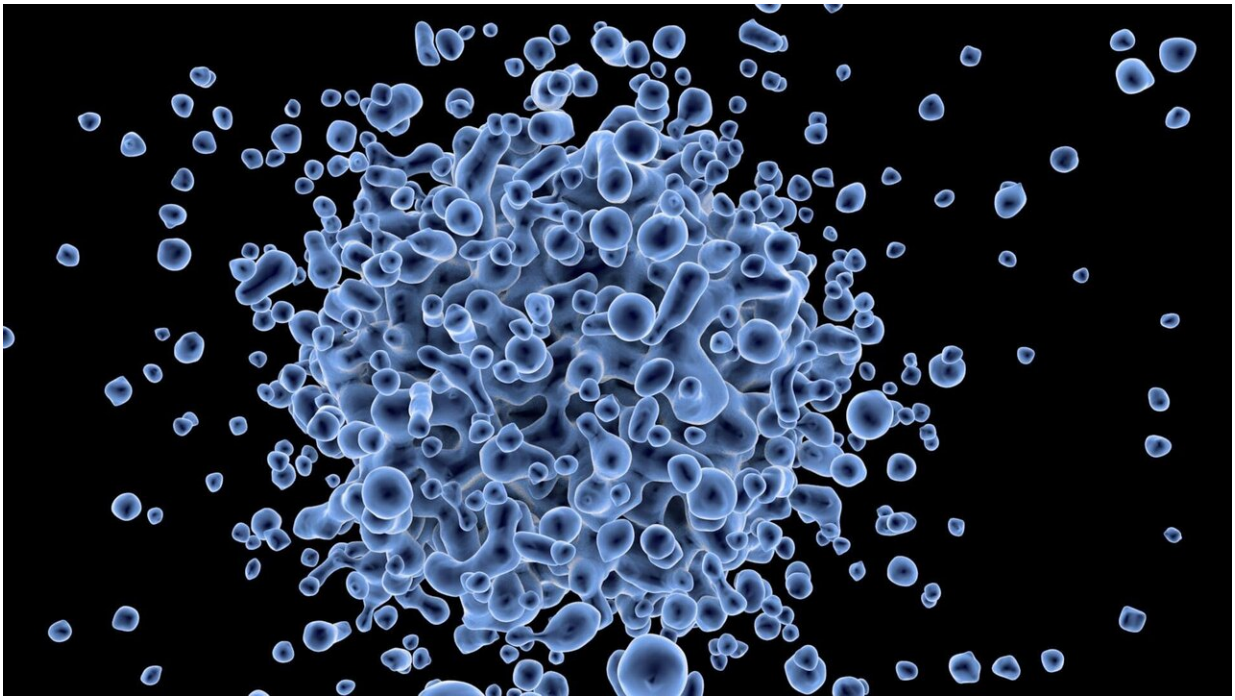

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The liver serves many critical functions within the human body, including the production of critical proteins, and the removal of waste and toxins. But when damage occurs to the largest organ in the body, many people do not experience symptoms until serious damage has occurred. When the liver becomes scarred, blood can collect and raise the pressure of the portal vein. This accumulation causes portal

hypertension and can lead to fluid build up in the abdomen and other detrimental side effects, including death.

In new research published in the *Journal of Experimental Medicine*, the research team led by Silvia Vilarinho, MD, Ph.D., assistant professor of medicine (digestive diseases), and of pathology, performed genomic analysis to determine the cause of unexplained portal hypertension in four unrelated families.

This paper is a culmination of over five years of work from Vilarinho's lab. "This is very exciting," said Vilarinho. "The excitement is to be going from patients that we didn't know why they develop portal hypertension, to the identification of a novel gene. This new information led us to determine what liver cell is affected and therefore uncover that portal hypertension in these patients resulted from alterations in liver endothelium. Since similar endothelial cell changes are seen in common forms of liver disease, these findings have the potential to actually translate into therapeutics for chronic liver disease."

The team evaluated nine patients from four families with unexplained portal hypertension and found that each affected person had a rare alteration in the same GIMAP5 gene. After the team replicated their findings using mouse models, they determined that recessive GIMAP5 genotypes resulted in the loss of normal GIMAP5 function and in turn, is an important regulator of liver endothelial cell homeostasis and in its absence, causes portal hypertension.

Vilarinho's lab will continue to evaluate the role of GIMAP5 in liver disease to determine the scope of the issue. "This is one of the main reasons I am passionate about a physician-scientist career. It is fascinating to uncover a new molecular mechanism that explains why certain individuals develop disease. We are interested to investigate whether this pathway is also important in common forms of liver

disease, and if yes, I think we could be on great things. If it's rare, we will still help people, just at a smaller scale," she said.

More information: Kaela Drzewiecki et al. GIMAP5 maintains liver endothelial cell homeostasis and prevents portal hypertension, *Journal of Experimental Medicine* (2021). DOI: 10.1084/jem.20201745

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