Possible genetic basis and mouse model found for severe nonalcoholic fatty liver disease

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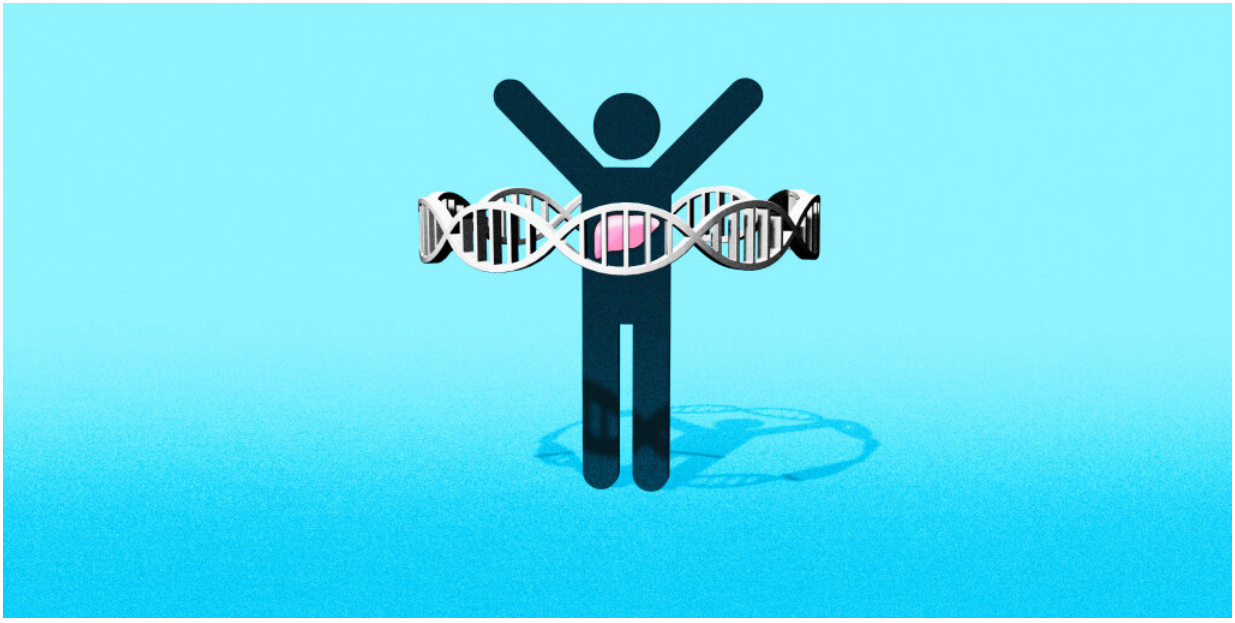


The SRSF1 gene acts as a guardian against DNA damage in the liver, University of Illinois Urbana-Champaign researchers found. When it is missing or inactivated, severe nonalcoholic fatty liver disease symptoms develop. Credit: Michael Vincent

A mutant or damaged gene may be a cause of a severe, mysterious form of nonalcoholic fatty liver disease, University of Illinois Urbana-Champaign researchers have found. Mice and human liver cells lacking

the SRSF1 gene show all the hallmarks of nonalcoholic steatohepatitis, also known as NASH, the researchers discovered.

The unique mouse model captures all three hallmarks of excess fat, inflammation and scarring in the liver, opening the doors to better understanding and development of treatments for NASH, said study leader Auinash Kalsotra, a biochemistry professor at Illinois. The researchers published their results in the journal *Nature Communications*.

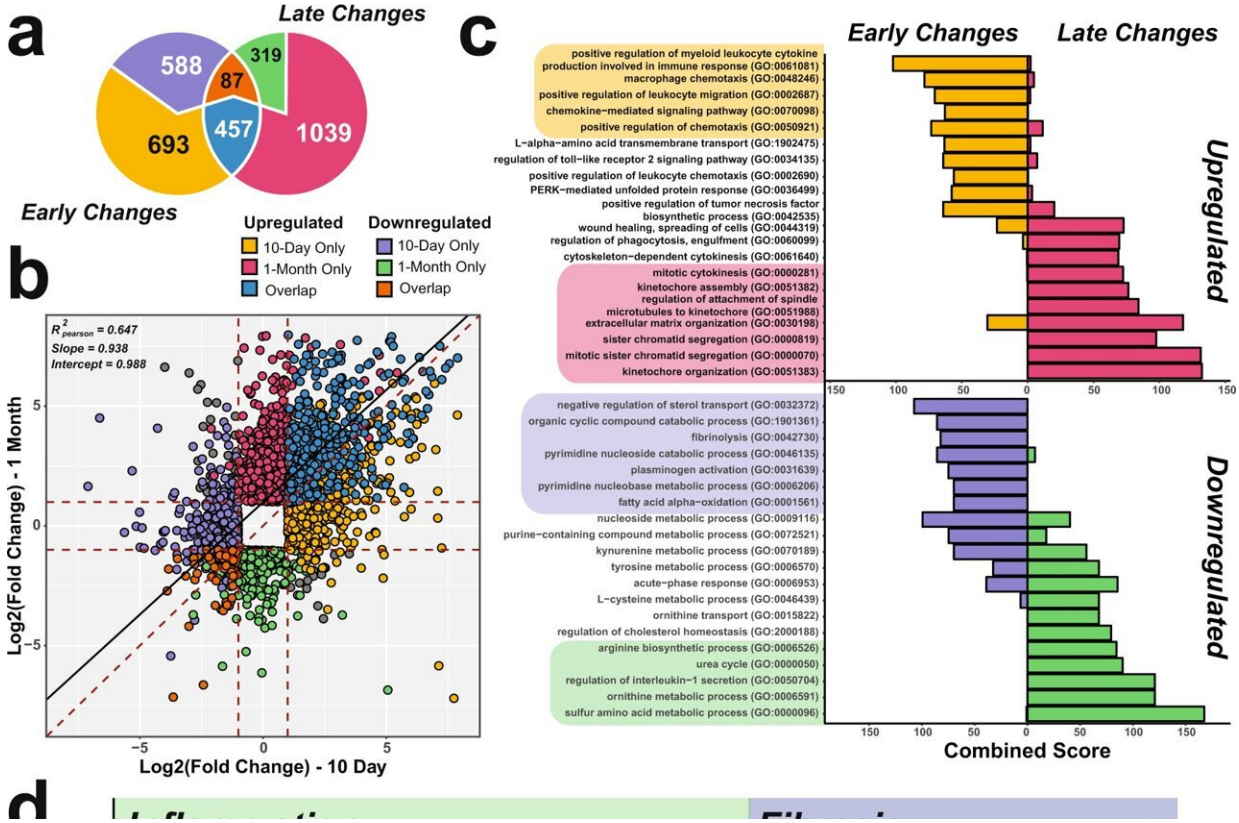
Nonalcoholic fatty liver disease affects an estimated 25% of Americans, according to the National Institutes of Health, and up to a third of patients will develop inflammation and scarring as well, falling under the NASH classification.

"It's not really clear why certain people end up developing NASH," Kalsotra said. "So far, there haven't been any genes that have been directly linked to NASH. It's been thought of as a progression: After the liver is injured or it becomes fatty, if you don't check it, it's going to progress toward NASH. But not everybody with fatty liver develops NASH and it seems random who does, so it's very confusing as to why this happens."

The other problem making NASH research difficult is the lack of good animal or cellular models for it, Kalsotra said. While some models incorporate one or two of the symptoms, and then other damage inflicted to mimic what is seen in NASH patients, they don't give an accurate portrayal of the disease.

Kalsotra's group began studying SRSF1, a protein that assists in splicing RNA in the cell, to study its splicing activity. They bred a line of mice that were lacking the gene to learn about its splicing activity. The mice soon spontaneously developed all the symptoms of NASH.

"We were very excited to see this, as we thought, this could be a model for the disease. But first, we had to figure out the mechanisms of why SRSF1 was connected to liver disease," said graduate student Waqar Arif, the first author of the study.



Gene expression signatures in SRSF1 HKO hepatocytes transition from an early inflammatory to a late fibrotic phase. a) Overlap of differentially expressed genes from RNA-seq (FDR

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