Mutations in novel gene found to be responsible for severe liver disease in children

August 2 2022

Image of the resected liver from a child with mutations in the FOCAD gene showing striking signs of cirrhosis, requiring liver transplant. Credit: A*STAR's Genome Institute of Singapore

New findings have uncovered how essential the FOCAD gene is for

maintaining a healthy liver, especially in children. In a research study published in *Nature Genetics*, scientists have found that children carrying loss-of-function mutations in FOCAD are presented with an early onset, pediatric form of liver cirrhosis that can be life-threatening. The study was carried out by scientists from A*STAR's Genome Institute of Singapore (GIS), in collaboration with hospitals and institutes across seven countries (India, U.S., Saudi Arabia, Pakistan, Portugal, Brazil, and France).

Liver disease is becoming a major health concern and is estimated to be the fifth most common cause of death worldwide. A systematic review from the Global Burden of Disease Study identified 1.32 million deaths due to liver cirrhosis in 2017, accounting for more than two percent of the total global deaths. Liver cirrhosis is usually diagnosed late in life, and is traditionally believed to be caused by environmental factors such as poor diet, viral hepatitis or alcohol abuse.

In collaboration with clinicians worldwide, the team combined classical tools such as Mendelian genetics and animal models with modern technology, such as deep sequencing and state-of-the-art gene editing tools to identify that the FOCAD gene is indispensable for maintaining liver health in humans. Mutations in this gene cause an early onset form of liver cirrhosis not documented before. The findings of a single gene, or monogenic, disorder that leads to cirrhosis in childhood establish a strong genetic component for liver disease, which was previously unknown.

In further analysis, they discovered that FOCAD functions as part of a molecular quality control mechanism that assists in translation, a fundamental cellular process by which proteins are made. The main cells of the liver, hepatocytes, were found to rely heavily on this mechanism compared to other cell types. This is the first time that this translation-dependent quality control machinery has been implicated in liver health.

The team also discovered a cytokine, CCL2, that is overproduced in FOCAD deficient patients and may play a key role in the progression of liver cirrhosis. Dr. Ricardo Moreno Traspas, a postdoctoral fellow from the Laboratory of Human Genetics and Therapeutics at GIS, and first author of the study, explained, "FOCAD mutations lead to an overproduction of a number of proteins that may be key drivers in the progression of the disease. One example is the signaling mediator, CCL2, that attracts immune cells and promotes liver inflammation. Drugs that target this, or similar candidates, are potential therapeutic intervention points for cirrhotic patients."

Prof. Bruno Reversade, Senior Group Leader at GIS and corresponding author of the study, commented, "We report the clinical impact of recessive loss-of-function variants in the FOCAD gene, and provide evidence for the importance of the SKI mRNA surveillance pathway for liver homeostasis. The research also brings forth the first animal model of the human disease, as well as in vitro biological systems that are now being used as platforms to identify and validate new anti-fibrotic therapeutic targets."

Prof. Patrick Tan, Executive Director of GIS, said, "The knowledge and tools generated in this study have the potential to aid in the development of innovative therapies for more common forms of liver diseases such as fatty liver disease and liver cancer. Our clinical data will also help clinicians to identify new patients with this syndrome, better understand the cellular and molecular mechanisms of the disease, and hence, provide a more accurate diagnosis, prognosis, and treatment."

More information: Ricardo Moreno Traspas et al, Loss of FOCAD, operating via the SKI messenger RNA surveillance pathway, causes a pediatric syndrome with liver cirrhosis, *Nature Genetics* (2022). DOI: 10.1038/s41588-022-01120-0

Provided by Agency for Science, Technology and Research (A*STAR), Singapore