Genetic cause of severe liver disease discovered

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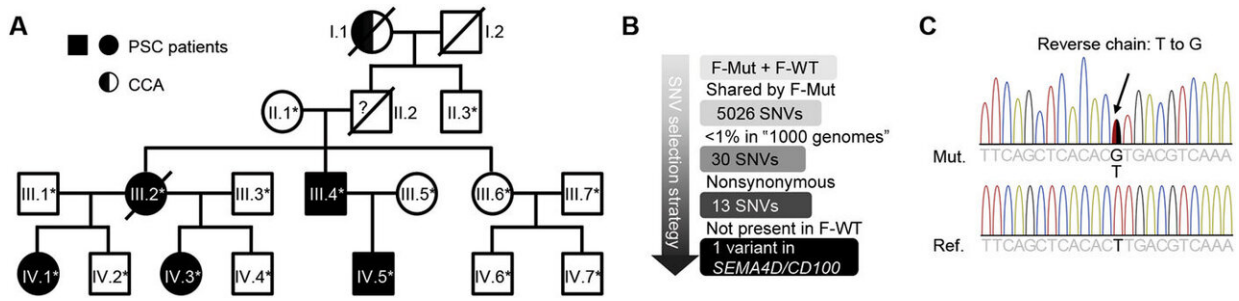

Fig. 1 Identification of a missense mutation in SEMA4D/CD100 in a family with PSC. (A) Pedigree of a family with PSC. Squares, male participants; circles, female participants; black filled symbols, patients with PSC; half-filled symbol, patient with cholangiocarcinoma (CCA) but without a confirmed diagnosis of PSC; crossed-out symbols, deceased participants. Whole-exome sequencing was carried out on participants with an asterisk. (B) Single-nucleotide variant (SNV) selection strategy. (C) Confirmation of the CD100K849T mutation by Sanger sequencing. F-Mut, family members with PSC; F-WT, healthy family members. Credit: *Science Translational Medicine* (2021). DOI: 10.1126/scitranslmed.abb0036

Primary sclerosing cholangitis, or PSC, is a rare chronic inflammatory disease of the bile ducts. It normally debuts in young adults and two thirds of patients are men. In most cases, the patient also has an inflammatory bowel disease, such as ulcerative colitis or Crohn's disease.

Liver transplantation is currently the only treatment available for the severe liver disease PSC. Now, however, researchers at Karolinska Institutet and Oslo University have discovered the first reported genetic mutation that causes PSC. The study, which is published in *Science Translational Medicine*, opens new paths to future treatments.

A family with PSC

Researchers at Karolinska Institutet and Oslo University have now described for what seems to be the first time a family with an autosomal dominant form of PSC, with five affected and 13 healthy family members. An autosomal dominant disease is an inherited disease that an individual can develop even if only one of the parents has the abnormal gene.

By analyzing the DNA of the family members, the researchers found a genetic mutation in the five patients that was not found in their healthy kin.

"The mutation localizes to a molecule that exists on the surface of many white blood cells, including immune system T cells," says Niklas Björkström, doctor and researcher at the Center for Infectious Medicine, Karolinska Institutet (Huddinge) and one of the study's senior authors.

Disrupted T cell function

The researchers re-created a genetic mutation in mice that was identical to that in the family members with PSC. The mice developed PSC-like symptoms, which suggests that the identified mutation actually caused the disease in the group under study.

Finally, the researchers managed to show that the mutation also

disrupted T cell function. When these cells were replaced with normal T cells, the mice bearing the mutation could return to health.

"This is a great step forward that helps us understand PSC," says Annika Bergquist, adjunct professor at the Department of Medicine, Karolinska Institutet (Huddinge), consultant at Karolinska University Hospital's gastroenterology unit and clinical researcher in charge of the study in Stockholm. "A treatment that stops the disease progressing is urgent, and a vital route to this end is learning more about the mechanisms behind this disease."

Their findings contribute to the first genetic explanation of PSC. Their focus now is on finding how the results can be used to develop new future treatments.

More information: Xiaojun Jiang et al. A heterozygous germline CD100 mutation in a family with primary sclerosing cholangitis, *Science Translational Medicine* (2021). DOI: 10.1126/scitranslmed.abb0036

Provided by Karolinska Institutet