Large-scale genetic study defines relationship between primary sclerosing cholangitis and other autoimmune diseases

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For the first time, scientists show that a leading cause of liver transplant, primary sclerosing cholangitis (PSC), is a distinct disease from inflammatory bowel disease, opening up new avenues for specific PSC treatments.

Researchers have newly associated nine genetic regions with a rare autoimmune disease of the liver known as primary sclerosing cholangitis (PSC). This brings the total number of genetic regions associated with the disease to 16.

Approximately 70 per cent of people who suffer from PSC also suffer from IBD. The team showed that only half of the newly associated genetic regions were shared with inflammatory bowel disease (IBD). For the first time, this definitively proves that PSC, although genetically related to IBD, is a distinct disease.

PSC is a chronic, progressive disease of the bile ducts that channels bile from the liver into the intestines. It can cause inflammation of the bile ducts (cholangitis) and liver scarring that leads to liver cirrhosis and liver failure. There are no effective treatments available. Although PSC affects only one in 10,000 people, it is a leading cause of liver transplant surgery.

"Before our study, it was never quite clear whether PSC was a

complication of IBD or a distinct disease in its own right," says Dr Carl Anderson, lead author from the Wellcome Trust Sanger Institute. "We have proven it to be a unique disease, and hope that our results will inform the development of more effective treatments, designed to target the biological pathways involved in causing the disease".

The work involved an international group of scientists from the International PSC study group recruiting patients from 13 countries within Europe and North America. Without this large collaborative effort it would not have been possible to obtain the large number of patient DNA samples necessary for the study.

The team used DNA genotyping technology to survey more thoroughly regions of the genome known to underlie other immune-related diseases to discover if they also play a role in PSC susceptibility.

In addition to the nine genetic regions newly associated, they also saw strong signals at three regions of the genome previously associated with the disease. Of these twelve genetic regions, six are also associated with IBD, while the six other regions showed little to no association in a recent large study of IBD.

"Using the Immunochip genotyping chip, we can pull apart the genetic relationships between these autoimmune diseases and begin to see not only their genetic similarities, but also the differences," says Jimmy Liu, PhD student and first author from the Wellcome Trust Sanger Institute. "As PSC is a rare disorder, sample collection is more difficult than for other, more common, autoimmune diseases. We hope that with more samples from patients, we'll be able to link more genetic regions to the disease, and it will become easier to identify underlying pathways that could act as therapeutic targets."

Three of the genetic regions associated with PSC fall within a single

biological system that underlies variation in T cells, cells important to our immune response. One gene that controls this pathway, HDAC7, is known to be a key factor in immune tolerance and the new data strongly suggests exploring the possibility that drugs affecting HDAC7 function may serve as future therapeutics in PSC.

In an extended analysis, the team identified an additional 33 genetic regions that are also involved in several common immune-mediated conditions (celiac disease, Crohn's disease, ulcerative colitis, type 1 diabetes, rheumatoid arthritis, sarcoidosis and psoriasis). This analysis shows that PSC shares many genetic risk loci with other immune-mediated diseases and opens up the possibility for testing drugs known to be effective in genetically similar diseases for efficacy in PSC.

The next step for the team is to do a high-powered search throughout the entire genomes of PSC patients to find specific regions associated with PSC outside of the regions included on the Immunochip genotyping chip.

"This study has uncovered more about the genetics underlying PSC than any before it, but this is only the first step" says Dr Tom Hemming Karlsen, lead author from Oslo University Hospital, Norway. "We hope the ongoing scientific and clinical research being conducted through the International PSC study group will help improve the outlook for those currently suffering at the hands of this disease"

"Our study, which is the largest of its type for PSC, would not have been possible without the help of the patients with this rare disorder," adds Dr Hemming Karlsen.

More information: Jimmy Z Liu, Johannes Roksund Hov, Trine Folseraas et al (2013) "Dense genotyping of immune-related disease regions identifies nine new risk loci for primary sclerosing cholangitis"

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