Researchers discover genetic cause for primary biliary cirrhosis

May 27 2009

Researchers have discovered a novel molecular path that predisposes patients to develop primary biliary cirrhosis, a disease that mainly affects women and slowly destroys their livers. Primary biliary cirrhosis has no known cause.

The finding, significant because it is a first step toward developing a targeted treatment and a cure, will be published in the June 11, 2009, issue of the *New England Journal of Medicine*.

"Now that we better understand the molecular basis of primary biliary cirrhosis, we can look for ways to specifically fix those elements," says Konstantinos Lazaridis, M.D., a Mayo Clinic hepatologist and a senior researcher in the study.

Currently, treatments for primary biliary cirrhosis can slow progression of the disease, which affects 1 in 2,500 Americans, 90 percent of them women. However, about half of patients do not respond to medical therapy. For some patients, a liver transplant cures the condition. But not all patients qualify for a transplant, and some transplant recipients experience a recurrence within five to 10 years.

The study was conducted at the University of Toronto using blood samples of patients collected at several medical centers in Canada and at Mayo Clinic's campus in Rochester, Minn., through its Primary Biliary Cirrhosis Genetic Epidemiology Research Resource. This resource comprises the biospecimens of hundreds of primary biliary cirrhosis

patients and individuals who do not have the disease (controls) --matched for age, sex, race and state of residence. Mayo Clinic and the University of Toronto are among the largest treatment centers in North America for primary biliary cirrhosis.

The University of Texas MD Anderson Cancer Center in Houston provided historical controls and conducted the statistical analysis of the study.

The genetic link to primary biliary cirrhosis has been well-established by previous studies. "Indeed, mothers, sisters and daughters in the same family have a significantly higher tendency to develop the disease compared with the general population," says Dr. Lazaridis.

To learn more about the cause of the illness, researchers designed a three-phase study to identify genetic markers associated with the disease. In phase one, researchers conducted a genome-wide association analysis, comparing the genotypes of 536 patients with primary biliary cirrhosis to those of 1,536 people who did not have the disease. Researchers looked at more than 300,000 single-nucleotide polymorphisms (SNPs), the most common genetic variations, among the approximately 11 million known to be present in the human genome.

"There were significant differences between the patients with primary biliary cirrhosis and the control group," says Dr. Lazaridis. As a result, researchers narrowed their focus to 16 SNPs significantly linked to primary biliary cirrhosis.

In phases two and three, researchers conducted "replication" and "fine-mapping" studies to confirm the initial results and to further detail the genetic variations most closely linked to primary biliary cirrhosis.

Researchers discovered that variants of two genes, interleukin 12A

(IL12A) and interleukin 12RB2 (IL12RB2), were strongly associated with primary biliary cirrhosis. These two genes constitute a pathway of the immune system. Potential therapeutic manipulation of this pathway provides new possibilities for more effective treatments of these patients, says Dr. Lazaridis.

Researchers also confirmed that the human leukocyte antigen (HLA) region of the genome is linked to primary biliary cirrhosis, an association which had been identified in previous research. "Although both the HLA region and the IL12 pathway are equally involved with susceptibility to primary biliary cirrhosis, HLA is very complicated to dissect genetically, with multiple pathways," says Dr. Lazaridis. "It will be difficult to modulate with the intention to treat, while IL12 is a single pathway and thus more amenable to treatment."

The reliability of the newly discovered association is very strong; statistically, there's about a one in 10 trillion chance that the pathway isn't linked to primary biliary cirrhosis, Dr. Lazaridis noted.

"That strong association is remarkable, given that the researchers started by looking at 300,000 genetic markers across approximately three billion base pairs that comprise our entire genetic material," he says. "Needle in a haystack doesn't begin to convey the challenge of this search."

Dr. Lazaridis describes this finding as the "end of the beginning" in learning more about the predisposing genetic factors to primary biliary cirrhosis. The newly discovered IL12 pathway does not account for all instances of primary biliary cirrhosis. There is more work to be done on additional genetic links, and exactly how IL12A and IL12RB2 contribute to primary biliary cirrhosis remains unknown. But researchers now have, for the first time, the knowledge to begin to develop targeted treatments and better predict outcomes for some patients with primary biliary cirrhosis.

Source: Mayo Clinic (news : web)