Gene study helps understand pulmonary fibrosis

April 16 2013

A new study looking at the genomes of more than 1,500 patients with idiopathic pulmonary fibrosis, a rare and devastating lung disease, found multiple genetic associations with the disease, including one gene variant that was linked to an increase in the risk of death.

The study, released early online in *The Lancet Respiratory Medicine*, showed that a variant in a gene called TOLLIP was associated with an increased mortality risk. That variant resulted in decreased expression of TOLLIP in the lungs of patients with idiopathic pulmonary fibrosis (IPF).

Because TOLLIP, also known as toll interacting protein, plays a role in regulating immunity to certain stimuli, this novel finding suggests that an abnormal immune response, possibly to infectious agents or even environmental injury, may be central to the disease.

Curiously, the version of TOLLIP that appears to prevent onset of the disease was also the variant that increased the risk of death in patients who did develop IPF.

"Our initial genome-wide study revealed 20 genetic loci that may be associated with this disease," said lead author Imre Noth, MD, professor of medicine and director of the Interstitial Lung Disease Program at the University of Chicago. "A more focused investigation showed that four of these play a crucial role."

The researchers confirmed one previously implicated gene tied to disease onset and, more important, found the new genetic locus that appears to play a role in both onset and mortality.

The results "change our perception of the importance of genetics in IPF," Noth said. "Preliminary work, looking at multiple variants of different genes, may allow us to predict the risk of death in IPF patients, which can vary according to their genetics up to 6.5 fold. This would be a powerful prognostic test."

Idiopathic pulmonary fibrosis affects about 150,000 people in the United States, usually after age 50. It causes progressive scarring of the lungs, which leads to increasing difficulty with breathing. For most patients, this leads to death, usually within three to five years. The only effective therapy is a lung transplant.

"The finding that one of the TOLLIP gene variants is reproducibly linked to higher mortality in IPF patients has significant implications for patient management," noted co-senior author Naftali Kaminski, MD, professor of medicine, Division of Pulmonary, Allergy and Critical Care Medicine, University of Pittsburgh School of Medicine, and director of UPMC's Dorothy P. and Richard P. Simmons Center for Interstitial Lung Disease.

"If an IPF patient has this variant, we might want to consider lung transplantation early in the course of the disease," he said. "It's not an ideal treatment, but it saves lives. We might be able to use the genetic markers to reveal who might need a transplant quickly, and to stratify patients for research."

One way to learn more about a complex disease such as IPF is through large-scale studies to search for genetic variations that are more common in those with the disorder. In many cases, the results of a single study are

not replicated.

To address this concern, the multi-institution research team looked for links between genetic markers and IPF in three separate cohorts of patients. The results were consistent in all three groups, highlighting the reproducibility of the results that could now provide investigators with a better understanding of what causes IPF.

"The findings of this study open new avenues for IPF research" noted co-senior author Joe G.N. Garcia, MD, professor and director of the Institute for Personalized Respiratory Medicine at the University of Illinois at Chicago and vice president for health affairs at the University of Illinois Hospital & Health Sciences System. "Researchers can now focus on understanding the role of the variants found in humans, and drug companies can assess whether they already have drugs that affect these pathways, thus shortening the lag to new therapeutics."

"IPF is a relentless disease for which we have no effective therapies to control or reverse the progressive scarring that leads to the untimely deaths," added James Kiley, PhD, Director of the Division of Lung Diseases at the National Heart, Lung and Blood Institute, part of the National Institutes of Health, which partially funded this study. "Insights from basic research like this are what we need to develop therapies that target the underlying disease process."

More information: The paper, "A Genome-wide Association Study Identifies Novel Genetic Variants in Association with Idiopathic Pulmonary Fibrosis Susceptibility and Mortality," will be published in the May issue of *The Lancet Respiratory Medicine.*

Provided by University of Chicago Medical Center