Common genetic variant linked to pulmonary fibrosis risk

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Scientists funded by the National Institutes of Health have identified a common genetic variant associated with substantially increased risk of developing pulmonary fibrosis, a debilitating and life-threatening lung condition. The genetic variant is found in a region of DNA thought to regulate the production of an important mucus-forming protein.

However, knowing the gene variant is not, by itself, enough for a test to determine who would be at risk of the disease, experts say.

This genetic variant near the mucin 5B gene, termed rs35705950, is both fairly common and a risk factor for idiopathic pulmonary fibrosis (IPF) and familial interstitial pneumonia (FIP). IPF and FIP are two related lung diseases that produce progressive, irreversible, and currently incurable scarring of the lungs, which is called fibrosis.

The study, published in the April 21 New England Journal of Medicine, compared the gene sequences of 575 individuals affected by IPF (492) or FIP (83) as well as 322 healthy people.

The researchers found that more than half of the IPF/FIP study participants have at least one copy of the variant, compared to one in six healthy controls who have the variant. Those with one copy have approximately five- to eightfold increased odds of developing fibrosis in their lungs, compared to those without the genetic variant. Individuals who have two copies of the variant have approximately twentyfold greater odds of developing fibrosis in their lungs.

"This study highlights how an investment in genomics can really pay off," said Susan Shurin, M.D., acting director of NIH's National Heart, Lung, and Blood Institute (NHLBI), one of the major funders of this research. "With this discovery we are one step closer to understanding these serious and mysterious diseases that affect over 100,000 Americans."

However, she cautioned that this variant alone cannot predict disease risk for an individual. Many people who have the variant still have healthy lungs, so genetic testing for rs35705950 alone is unlikely to help doctors to diagnose their patients. As yet unknown modifying genetic and/or environmental factors are likely to affect development of disease in persons who possess the genetic variant.

Since the risk of IPF or FIP in the general population is low, the absolute risk – the likelihood that an individual will have the condition – is still low, even for those with the variant.

Nevertheless, this discovery has immediate importance for scientists who study pulmonary fibrosis, since it may point to the root causes of IPF and FIP and to new ways to prevent and manage these conditions.

The genetic alteration identified by the multi-institution research team, led by researchers at National Jewish Health in Denver, occurs in a region called the promoter, near the mucin 5B gene. The promoter region regulates gene expression, and the identified variant ramps up the production of mucin 5B protein, causing normal lungs to produce over 35 times as much of this mucus-forming protein compared to controls.

"This possible association between mucus production and fibrosis shows how these new genomic technologies can open up new ways of thinking about diseases," said James Kiley, Ph.D., director of NHLBI's Division of Lung Diseases. "Down the road, this discovery will help us uncover

how pulmonary fibrosis develops, and potentially lead to new treatments."

More information: What is Idiopathic Pulmonary Fibrosis? www.nhlbi.nih.gov/health/dci/D … /ipf/ipf_whatis.html

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