National Jewish Health
Breathing Science is Life.

Genetic Discovery Offers New Hope in Fight Against Deadly Pulmonary Fibrosis

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DENVER — A team led by researchers at National Jewish Health has discovered a new genetic variation that increases the risk of developing pulmonary fibrosis by 7 to 22 times. The researchers report in the April 21, 2011, issue of *The New England Journal of Medicine* that nearly two-thirds of patients with idiopathic pulmonary fibrosis or familial interstitial pneumonia carry the genetic variation. It is associated with the *MUC5B* gene, which codes for a mucus-forming protein.

“This discovery not only identifies a major risk factor for pulmonary fibrosis, but also points us in an entirely new direction for research into the causes and potential treatments for this difficult disease,” said Max Seibold, PhD, first author and research instructor at National Jewish Health and the Center for Genes, Environment and Health. “The research also demonstrates how a genetic approach to disease can uncover a previously unknown and unsuspected association disease.”

Idiopathic pulmonary fibrosis (IPF) and familial interstitial pneumonia (FIP) are similar, invariably fatal diseases that involve progressive scarring of the lungs. The scarring prevents oxygen transport to the tissues, and most people die of respiratory failure within a few years of diagnosis. The diseases are relatively rare, but account for approximately 40,000 deaths each year, the same number as die of breast cancer. There is no approved treatment for the diseases.

Research into pulmonary fibrosis has been quite difficult. Little is understood about the biological roots of the diseases, and recent clinical trials of several experimental medications have failed to effectively treat them. Previous research has focused primarily on the scarring and inflammatory processes evident in the disease.

In the study funded by the National Heart, Lung and Blood Institute, National Jewish Health researchers and their colleagues took an “agnostic” approach, statistically analyzing the entire genome of 82 afflicted families. They found an association with the diseases in a region of chromosome 11 that contains four mucin genes involved in the production of mucus. Narrowing their search with fine mapping, then sequencing, they eventually found a common variation near the MUC5B gene, presumably in a regulatory element, that is strongly associated with the disease.

“This research suggests that mucus production where the small airways and the air sacs converge may play a significant role in pulmonary fibrosis,” said senior author David Schwartz, MD, Chair of the Department of Medicine at the University of Colorado School of Medicine and Director of the Center for Genes, Environment and Health at National Jewish Health.

The variation exists in 19 percent of healthy controls, 59 percent of FIP patients, and 67 percent of IPF patients. Carrying one copy of the gene increases the risk of developing FPF by 6.8 times, and IPF by 9.0 times. Carrying two copies of the variation increases risk 20.8 times and 21.8 times, respectively.

The researchers discovered that the genetic variant increases production of MUC5B more than thirtyfold in unaffected patients. They also found that MUC5B production is elevated in pulmonary fibrosis patients both with and without the gene.

“There are several biologically plausible ways in which excess mucus could cause disease,” said Dr. Schwartz. “We are currently investigating all of these mechanisms as potential causes of disease.”

Mucus is a vital part of lung biology, protecting delicate cells from direct exposure to inhaled irritants and toxins, and helping to clear them from the lungs. The researchers hypothesize that excess mucus production caused by the MUC5B variant could slow clearance of mucus contaminated with irritants and toxins. Excess mucus might also interfere with repair of air sacs damaged by these contaminants. Another scenario suggests that the genetic variation could trigger the production of mucus in areas where it is not normally present.

In addition to National Jewish Health, other institutes contributing to this study were the University of Colorado School of Medicine, Colorado School of Public Health, Duke University Medical Center, North Carolina State University, Vanderbilt University School of Medicine, Landspitali University Hospital, in Reykjavik, Iceland, the University of Texas M. D. Anderson Cancer Center, the University of Miami, and the National Institute of Environmental Health Sciences.

National Jewish Health is known worldwide for treatment of patients with respiratory, cardiac, immune and related disorders, and for groundbreaking medical research. Founded in 1899 as a nonprofit hospital, National Jewish Health remains the only facility in the world dedicated exclusively to these disorders. Since 1998, U.S. News & World Report has ranked National Jewish the #1 respiratory hospital in the nation.

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