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Genome Study Suggests New Strategies for Understanding and Treating Pulmonary Fibrosis

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DENVER — A new genome-wide association study of more than 6,000 people has identified seven new genetic regions associated with pulmonary fibrosis. In findings published online in *Nature Genetics* on April 14, 2013, researchers at National Jewish Health, the University of Colorado and several other institutions found a number of genes associated with host defense, cell-cell adhesion and DNA repair, which provide clues to possible mechanisms underlying this currently untreatable disease.

“This research gives us several new targets for investigation of pulmonary fibrosis,” said David Schwartz, MD, senior author on the paper, Professor of Medicine at National Jewish Health and Chair of Medicine the University of Colorado School of Medicine. “We believe that there are several relatively common genetic risk factors, which combine with repeated lung injury to cause this devastating lung disease.”

Pulmonary fibrosis is a potentially deadly scarring of lung tissue. Although there are a number of known contributors to its development, most cases have no known cause. Without an approved medical therapy, patients with the most common form, idiopathic pulmonary fibrosis, survive an average of only two to three years after diagnosis.

“Pulmonary fibrosis has resisted our attempts to find a clearly beneficial treatment,” said co-author Kevin K. Brown, MD, Vice Chair of Medicine at National Jewish Health. “This study gives us new insights into how the disease develops. By better understanding this, we can better focus future therapies.”

Researchers from more than 20 institutions, led by National Jewish Health and the University of Colorado, confirmed three previously reported genetic risk factors and identified seven new ones, which together account for about one-third of the disease risk.

The team’s findings confirmed the risk associated with specific changes in *MUC5B*, a gene that produces a protein in mucus. Researchers believe variations in this gene may lead to pulmonary fibrosis by interfering with mucosal defense, repair of lung alveoli or direct toxicity to cells.

The researchers also found stronger evidence for the role of telomeres, a protective section of DNA located at the tips of chromosomes. Shorter telomeres are associated with a reduced ability to divide and premature cell death. Previously, two rare genetic mutations had been associated with some forms of pulmonary fibrosis. The research team found common variants in and near those two genes, and a common variant in another gene.

The researchers also identified three genes associated with connections that hold adjoining cells together, known as cell-cell adhesion. Impaired cell-cell adhesion can lead to lost tissue integrity.

These findings support the researchers’ belief that pulmonary fibrosis may be influenced by different genes in different people. Careful genotyping could identify different forms of the disease, allowing for more effective, individualized therapy.

The research was supported by the National Heart, Lung and Blood Institute (NHLBI). “In addition to expanding the library of genetic changes that can underlie pulmonary fibrosis, this study’s findings demonstrate that both rare and common genetic variants contribute significantly to pulmonary fibrosis risk,” said James Kiley, PhD, Director of NHLBI’s Division of Lung Diseases. “A key next step for research is figuring out how these genetic variants work with environmental factors in the development of the disease.”

National Jewish Health is the leading respiratory hospital in the nation. Founded 121 years ago as a nonprofit hospital,

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