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# Study identifies genome regions that could influence severity of cystic fibrosis

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A team of researchers, including a number from the University of North Carolina at Chapel Hill School of Medicine, have pinpointed regions of the genome that contribute to the debilitating lung disease that is the hallmark of cystic fibrosis.

Their findings provide insight into the causes of the wide variation in lung disease severity experienced by CF patients. It also points the way to new diagnostic markers and therapeutic approaches for this and more common lung diseases such as COPD.

This study, which appears online Sunday, May 22, 2011 in the journal *Nature Genetics*, is among the first reported genome-wide scans of a single gene disorder. It was the work of the North America CF Gene Modifier Consortium, which brought together dozens of investigators from the United States and Canada to identify which regions of the genome are associated with lung disease severity in almost 3,500 CF patients.

"This cystic fibrosis discovery showcases the valuable information that can be obtained when scientists work together on genome wide association studies," said Susan B. Shurin, MD, acting director of the NHLBI. "Now we are closer to understanding why patients with the exact same genetic mutation in the cystic fibrosis gene have such widely varying manifestations of lung disease, and closer to finding new therapies."

CF is a genetic disease that causes the lungs to clog up with thick, sticky mucus that is prone to infection. Though every CF patient carries mutations in both copies of the same gene – coding for a protein called cystic fibrosis transmembrane conductance regulator or CFTR – symptoms can vary widely from patient to patient. For instance, some patients can have such severe lung disease that they are near death at the age of 10, whereas others can have nearly normal lung function at the age of 35.

"There is very good reason to believe that what we have discovered in CF lung disease could apply to other diseases as well," said one of the senior study authors Michael Knowles, MD, professor of pulmonary and critical care medicine at UNC. "Just as an example, a previous study of our Consortium, led by Scott Blackman MD, PhD, uncovered a gene called TCF7L2 associated with diabetes in CF patients. Genetic variation in TCF7L2 is the strongest common genetic variant associated with risk for type 2 diabetes in the general population."

For the last decade, Knowles and his colleagues have been searching for other genetic factors that modify the effects of the disease-causing mutations in the CFTR gene, improving or exacerbating the disease as it unfolds. One way they have looked for these potential "genetic modifiers," has been through a candidate gene approach, methodically hand-picking their most likely candidates from the 20,000-some genes in the human genome. But that approach could be missing some key players.

"Going after those candidate genes means relying on past basic and clinical data, and in some cases chasing ghosts and half-truths," said lead study author Fred Wright, PhD, professor of biostatistics at UNC. "But when you step back and scan the entire genome, it is an unbiased look at what is there. In fact, both of the most significant genome-wide regions that we uncovered in this study are not ones that we would have

necessarily predicted."

Genome-wide association studies use "genechip" technology to identify genetic variants (single gene polymorphisms or "SNPs") that could explain differences in health between individuals. The Consortium tested DNA from 2,464 CF patients, and then replicated their findings in another of 973 patients. They also performed a separate genome-wide linkage scan, which looks at how gene variants are inherited through multiple affected families. All of their results pointed to the same two regions of the genome, one on chromosome 11 and one on chromosome 20.

Members of the consortium have now divvied up these chromosomal hotspots and are trying to understand how variants in these regions could underlie CF progression. For his part, Knowles plans to focus on chromosome 11, which contains genes relevant to airway cell function.

"The great expectation is that once we have a handle on a few key genes that contribute to the variation we see in the clinic then we have a great starting point to find mechanisms and biological pathways that may make good targets for treating lung disease," said Wright.

Provided by University of North Carolina School of Medicine