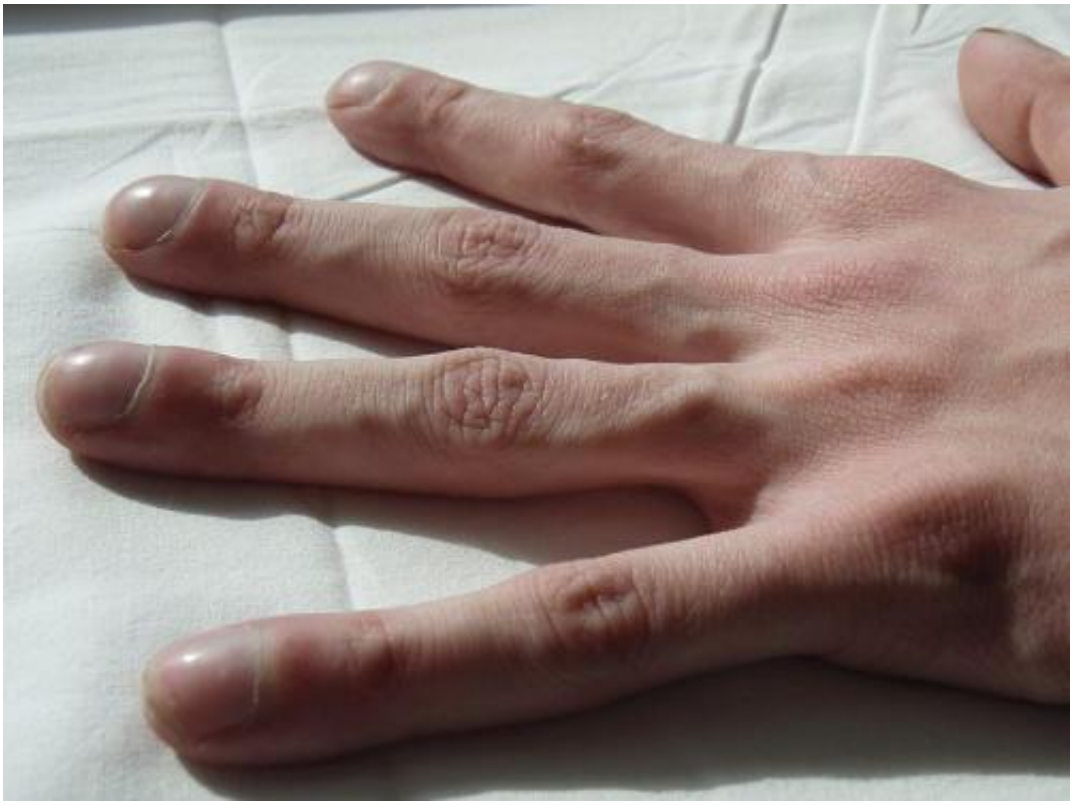
Five genetic regions implicated in cystic fibrosis severity

September 29 2015



"Clubbing" of the fingers is a classic features of Cystic Fibrosis, although not present in many patients. Credit: Jerry Nick, M.D./ Wikipedia

If you have two faulty copies of the CFTR gene, you will have cystic fibrosis. But the severity of your disease will depend on environmental factors and many other genes. Locating these genes and altering their function could lead to new therapies. Now, a consortium of research

institutions in the United States, Canada, and France report that five regions of the human genome are home to the genetic variations that play major roles in CF disease severity.

Already, as a result of this multi-year project, researchers at the University of North Carolina School of Medicine / UNC Marsico Lung Institute and Case Western University are lab-testing drugs against targets that relate to two of these regions. Researchers believe these drugs have the potential to improve lung disease in some CF patients.

The study, published today in *Nature Communications*, is the largest-ever genome-wide association study of cystic fibrosis or any other rare disease. Samples from 6,365 people with cystic fibrosis (CF) were collected over the course of several years at dozens of cystic fibrosis centers in order to make this project possible.

"It has been an unprecedented undertaking to enroll this many patients and have this kind of data output," said Michael Knowles, MD, professor of pulmonary and critical care medicine at UNC and one of three senior co-authors. "It's mind-boggling that five regions of the genome pop out of all this data from millions of SNPs - [single nucleotide polymorphisms or genetic variations] - that we analyzed."

Now, the consortium is homing in on ways to influence these genetic locations to benefit CF patients.

"I am excited to see the fruits of this project that began in 2000," said Preston Campbell, MD, executive vice president for medical affairs for the Cystic Fibrosis Foundation. "Identifying the genetic underpinnings for differences in CF lung disease will hopefully inform our precision medicine efforts and spur further drug development."

CF is a genetic disease that causes thick, sticky mucus to build up in the

lungs. This build-up makes patients more susceptible to infections, such as pneumonia. Over the past two decades, Better therapies have increased life expectancy for many patients, but disease severity varies widely even among patients with the exact same CFTR gene mutation. For instance, a six-year old could have severe disease, poor lung function , and endure multiple hospitalizations while a 25-year old may have nearly normal lung function and never be hospitalized until much later in life. The difference lies, in part, in these five genetic regions that the consortium's 12-year research project uncovered.

This work is integral for CF patients because moderately improving the function of the CFTR gene, alone, won't necessarily be enough to optimize lung function for most people with the disease.

A new CF drug was introduced in July. It was designed to "fix" the Delta-F mutation - the most common CFTR mutation. But the drug does not provide a complete fix. And for some people with the Delta-F mutation, the drug doesn't work at all.

"The reason lies in part in these modifier genes found within the five genome locations we've identified," said Garry Cutting, MD, professor of pediatrics and medicine at Johns Hopkins and senior co-author of the *Nature Communications* paper. "Some of these genes create proteins that have a functional interaction with the CFTR gene, or have complementary roles to protect the lung against ongoing damage. They play important supporting roles to make sure the CFTR protein and other proteins and protective mechanisms work properly. We need to influence these modifier proteins in order to lessen the severity of disease for patients."

The International CF Modifier Consortium - which is led by researchers from UNC, the University of Toronto, Johns Hopkins University, Case Western University, and the University of Paris - analyzed more than 8.5

million SNPs - or DNA sequence variations - over the span of 12 months to find the five genetic locations on chromosomes 3, 5, 6, 11, and X that were significantly associated with variation of lung disease.

The consortium is now trying to link these genetic polymorphisms to gene expression - the amounts of proteins that genes create. This would allow them and other researchers to design more targeted therapies to lessen disease severity, decrease infections and hospitalizations, and prolong life.

Lisa Strug, PhD, senior co-author, associate profess or biostatistics, and senior scientist in the Program in Genetics and Genome Biology at the Hospital for Sick Children in Toronto, said, "The ongoing work of the consortium to discover and translate genetic determinants of disease variability in cystic fibrosis is leading to personalized therapeutic approaches to improve outcomes for all individuals with the disease."

Provided by University of North Carolina Health Care