Medical Xpress

Severity of cystic fibrosis may be determined by presence of newly-identified modifier genes

May 25 2011, By Suzanne Gold

(Medical Xpress) -- In an age where personalized medicine is within reach, a one-size-fits-all approach just won't cut it. A group of North American researchers have identified two "modifier" genes in the genomes of cystic fibrosis patients that may be responsible for variation in severity between patients. This is the first study to show evidence that modifier genes affect lung disease severity in cystic fibrosis.

The scientists set out to find out why some cystic fibrosis patients had a good quality of life, while others who carried the same mistakes in their cystic fibrosis genes were experiencing severe lung disease, were in need of lung transplants, or died. Their discovery of modifying genes may eventually lead to tailoring treatment to patients according to their individual disease. The study is reported in the May 22 advance online edition of *Nature Genetics*.

Nearly a decade ago, the Canadian team, led by U of T Professor Peter Durie (who is based at The Hospital for Sick Children (SickKids)), teamed up with researchers and 37 cystic fibrosis clinics across the country and obtained DNA and information about the lungs, intestine, liver and pancreas of 75 per cent of the Canadian cystic fibrosis population. After discovering that their colleagues at the Johns Hopkins University School of Medicine and the University of North Carolina at Chapel Hill were doing similar studies, the three teams decided to form the North American Cystic Fibrosis Gene Modifier Consortium and

joined forces with other centres across the continent in a genome-wide association study involving more than 3,400 patients.

“We discovered that people with cystic fibrosis didn’t necessarily show predictable disease progression patterns,” said Durie, a professor of pediatrics, a member of U of T’s Institute of Medical Sciences and a lead investigator of the Canadian Consortium for Cystic Fibrosis Genetic Studies. “If you look at the lung function of patients, even those that inherited identical mutations in the cystic fibrosis gene, disease severity and lung function decline can differ substantially. We know that these patients all have cystic fibrosis, but the rate at which their lungs are deteriorating is variable.”

Back in 1989, SickKids scientists discovered the cystic fibrosis transmembrane conductance regulator (CFTR) - the gene that causes the disease. In cystic fibrosis, two copies of the abnormal and established causal gene must be present for the disease to develop. In the new study, researchers were able to identify regions on chromosomes 11 and 20 that influence the severity of lung disease and its progression.

Durie noted this is a major step toward therapeutic targets for patients with cystic fibrosis and other diseases. “This is a paradigm shift in how to approach treating a disease. Historically, we have treated the consequences of the disease - the symptoms and secondary infections that develop - but we are now looking at treating the basic contributors to the disease at a genetic level. If we understand what the genes are, we can find ways to tweak the genes or the protein products using drugs.”

This work was achieved by a strong collaborative effort by members of the Canadian Consortium for Cystic Fibrosis Genetic Studies research, which includes Drs. Lisa Strug, Mary Corey, Ruslan Dorfman and Julian Zielenski at SickKids, Lei Sun at the University of Toronto, Yves Berthiaume at the University of Montreal and Peter ParÃ© and Andrew

Sandford at the University of British Columbia.

In some Canadian provinces, cystic fibrosis is being diagnosed by newborn screening, so patients can be monitored even before they show the first signs of lung disease. The ultimate goal is to be able to predict the severity of cystic fibrosis disease of each individual before they get symptoms and to tailor their treatment based upon knowledge of their genetic makeup, thus preventing progression of the disease.

Cystic fibrosis is one of the most common inherited chronic lung diseases, affecting one in every 3,600 children born in Canada. It is characterized by a build-up of mucus in the lungs and in the ducts of the pancreas, causing breathing and digestion problems.

Provided by University of Toronto

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