DNA from cystic fibrosis patients with and without chronic infections points to unsuspected mutation

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This is a University of Washington exome sequencing lab where scientists analyze and compare protein-coding regions genomes. Credit: Clare McLean

(Medical Xpress) -- Comparing the DNA from patients at the best and worst extremes of a health condition can reveal genes for resistance and susceptibly. This approach discovered rare variations in the DCTN4 gene among cystic fibrosis patients most prone to early, chronic airway infections.

The DCTN4 gene codes for dynactin 4. This protein is a component of a molecular motor that moves trouble-making microbes along a cellular conveyer belt into miniscule chemical vats, called lysosomes, for annihilation.

This study, led by the University of Washington, is part of the National Heart Lung and Blood Institute GO Exome Sequencing Project and its Lung GO, both major National Institutes of Health chronic disease research efforts.

Similar "testing the extremes" strategies may have important applications in uncovering genetic factors behind other more common, traits, such as healthy and unhealthy hearts.

The results of the cystic fibrosis infection susceptibility study appear this Sunday, July 8, in Nature Genetics.

An exome sequencing lab in the UW Department of Genome Sciences. Image: Clare McLean

The infection in question was Pseudomonas aeruginosa, an opportunistic soil bacterium that commonly infects the lungs of people with cystic fibrosis and other airway-clogging disorders. The bacteria can unite into a slithery, hard-to-treat biofilm that hampers breathing and harms lung tissue. Chronic infections are linked to poor lung function and shorter lives among cystic fibrosis patients. These bacteria rarely attack people with normal lungs and well-functioning immune systems.

In the study, these rare variations in DCTN4 did not appear in any of the cystic fibrosis patients who were the most resistant to Pseudomonas infection. The study subjects most susceptible to early, chronic infection had at least one DCTN4 missense variant. A missense variant produces a protein that likely can't function properly.

The lead author of the report published July 8 in Nature Genetics is Mary J. Emond, research associate professor of biostatistics at the University of Washington School of Public Health in Seattle. The senior author is medical geneticist Michael Bamshad, UW professor of pediatrics in the Division of Genetic Medicine.

To the extent of their knowledge, the researchers think that this might be the first time that genetic variants underlying complex trait were discovered by sequencing all the protein-coding portions of the genomes of people at each extreme of a disease spectrum.

"We did not have a candidate gene in mind when we did this study," said Emond. Statistical analysis of the DNA of 91 patients led the research team to this particular gene. Of the initial study group, 43 children had their first onset of chronic lung infection with Pseudomonas as when they were very young, and the 48 oldest individuals had not yet reached a state of chronic infection. The patients selected for sequencing were

from the Early Pseudomonas Control (EPIC) Observational Study, a project at the Seattle Children's Research Institute, and the North American Cystic Fibrosis Genetic Modifiers Study. Exome sequencing was done by UW researchers in the laboratory of Deborah Nickerson, UW professor of genome sciences.

Comparisons of the protein coding portions of the study subjects' DNA called the researchers attention to missense variations of the DCTN4 gene. The researchers went on to screen a selected group of 1,322 other EPIC participants to check their findings.

Exome Sequencing Project scientists are using an approach similar to the one in this study to examine the genetics behind resistance and susceptibility to other chronic conditions like obesity, heart attacks and hypertension. They plumb for gene variations linked to heart disease, for example by putting DNA maps from people with ideal cholesterol levels up against those from people with exceptionally poor levels.

Adapting a similar strategy to determine the genetics underlying other complex human traits may require exome sequencing of a much larger sample sizes, the researchers noted.

"As the costs of exome sequencing are dropping rapidly and more efficient statistical analysis is becoming available, we think medical researchers' enthusiasm for this approach will continue," Bamshad predicted.

More information:
http://http//www.nature.com/ng/journal/vaop/ncurrent/pdf/ng.2344.pdf

Provided by University of Washington