Why do some people with cystic fibrosis live much longer than others?

Posted on October 24, 2017 by Kat J. McAlpine
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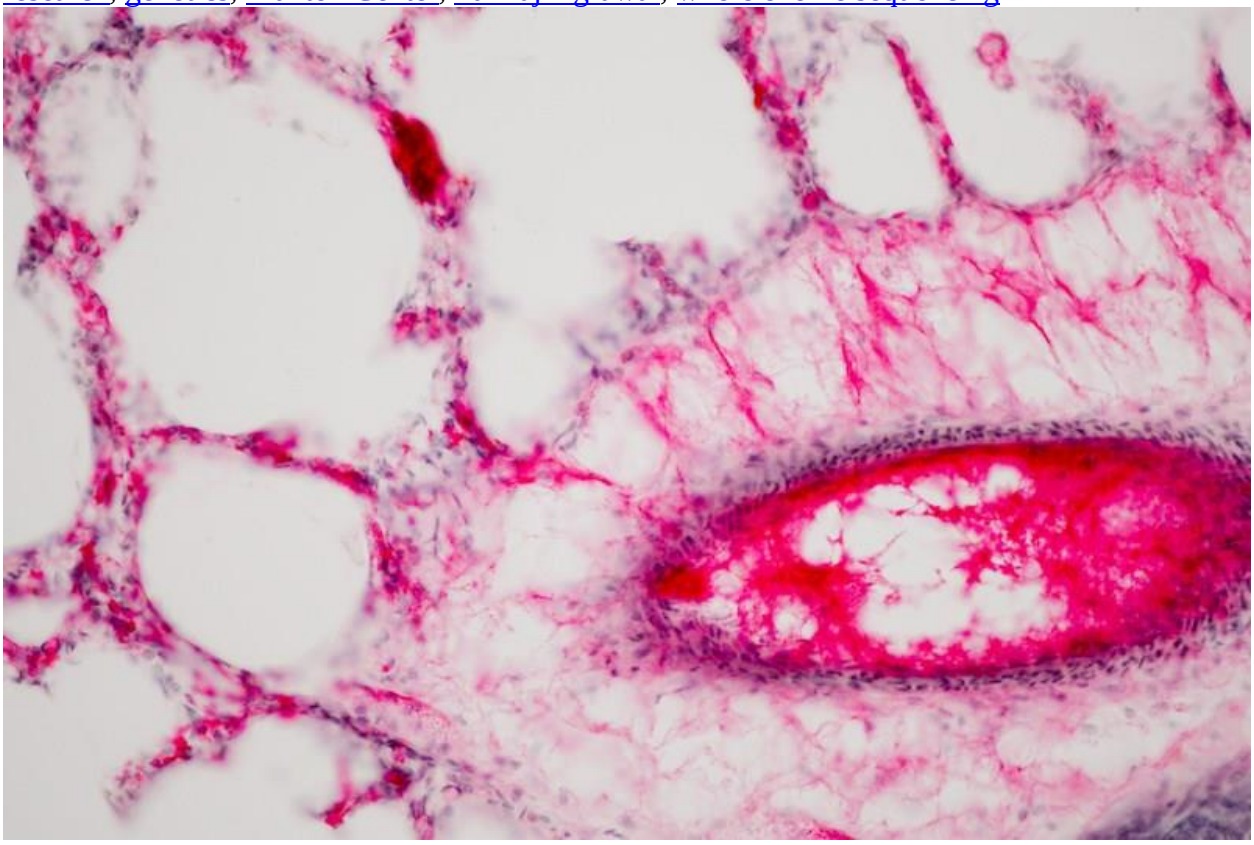

Lung tissue under microscope.

The answer may be hidden in their genes.

Cystic fibrosis is an inherited disorder caused by genetic mutations that disrupt the normal movement of chloride in and out of cells. Among other health problems, cystic fibrosis compromises the lungs' ability to fight infection and breathe efficiently, making it the most lethal genetic disease in the Caucasian population. Patients have an average lifespan of just 30 to 40 years.

Despite this narrow average lifespan, there is a big range in how severely cystic fibrosis (CF) affects the lungs and other organs depending on an individual's specific genetic variation, and even in how long patients sharing the same, most common genetic mutation are able to survive with CF.

This led researchers at Boston Children's Hospital to wonder if other genetic mutations could be protective against CF's effects. Recent findings published in the *American Journal of Respiratory Cell and Molecular Biology* suggest that may be the case.

"There are some patients at one end of extreme severity who need a lung transplant very early in life, then others whose clinical presentation seems to stabilize so that they can live into the fifth and sixth decades of life," says Pankaj Agrawal, MBBS, MMSc, principal investigator and medical director of The Manton Center's Gene Discovery Core at Boston Children's, who was the co-first author on the study.

To find out why, Agrawal and researchers at Boston Children's — including Ruobing Wang, MD, a pulmonologist, and Craig Gerard, MD, PhD, chief of the Division of Respiratory Diseases — conducted the first-ever longitudinal analysis of genetic modifiers related to CF.

They combed through a population of nearly 600 CF patients registered at the Boston Children's Cystic Fibrosis Center and found five individuals who stood out because of their advanced age — in their 50s or 60s — and relatively normal lung function.

"Given the large size of our center's patient population, we were able to find a number of individuals at this rare 'extreme,'" says Wang, who was co-first author on the paper.

A new hypothesis for mitigating cystic fibrosis

To discover the genetic variants, the researchers collected blood from these patients and performed whole exome sequencing on their DNA, analyzing the "coding" section of the genome that is responsible for most disease-related mutations.

Find more news about cystic fibrosis research at Boston Children's.

Sequencing the genes of these five Boston Children's patients — a cohort known as "long-term non-progressors"— the researchers found a set of rare and never-before-discovered genetic variants that might help explain their longevity and stable lung function.

The gene variants are related to so-called epithelial sodium channels (ENaCs), semi-permeable cellular pathways responsible for reabsorbing sodium in the kidney, colon, lung and sweat glands.

"Our hypothesis is that these ENaC mutations help to rehydrate the airways of CF patients, making it less likely for detrimental bacteria to take up residence in the lungs," says Wang.

The discovery brings ENaCs into the limelight as a potential new therapeutic target.

"For example, if we could target ENaCs with a small molecule or an antibody-based drug, we might be able to incur a protective effect against CF's progression," says Agrawal, who is also a physician in the Boston Children's Division of Newborn Medicine.

Based on their findings, the team is now doing further studies to analyze the genetics of patients at the other end of the CF spectrum — those with extremely severe clinical presentation of symptoms at a young age.

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In addition to Agrawal, Wang and Gerard (who was senior author), additional authors on the study are: Hongmei Lisa Li, Klaus Schmitz-Abe, Chantelle Simone-Roach, Jingxin Chen, Jiahai Shi, Tin Louie, Shaohu Sheng, Meghan C. Towne, Christine F Brainson, Michael A Matthay, Carla F. Kim, Michael Bamshad, Mary J. Emond, Norma P. Gerard and Thomas R Kleyman.

This work was supported by the Gene Discovery Core of The Manton Center for Orphan Disease Research, Boston Children's Hospital; Gilda and Alfred Slifka, Gail and Adam Slifka and the CFMS Fund; the National Institute of Arthritis and Musculoskeletal and Skeletal Diseases; the National Institute of Health (NIH) (U54 HD090255, P30 DK079307); the Eunice Kennedy Shriver National Institute of Child Health and Human Development/National Human Genome Research Institute/NIH (U19 HD077671); the May Family Fund; Cystic Fibrosis Foundation Therapeutics, Inc. (RO1 HL090136 and U01 HL100402 RFA-HL-09-004); and the National Heart, Lung, and Blood Institute (R37HL51856).