McGowan Institute for Regenerative Medicine
A program of the University of Pittsburgh and UPMC

Study Suggests Cystic Fibrosis Is Two Diseases, One Doesn't Affect Lungs

Cystic fibrosis (CF) could be considered two diseases, one that affects multiple organs including the lungs, and one that doesn't affect the lungs at all, according to a multicenter team led by researchers at the University of Pittsburgh School of Medicine. The research, led by co-senior investigator McGowan Institute for Regenerative Medicine affiliated faculty member David Whitcomb, M.D., Ph.D., chief of gastroenterology, hepatology and nutrition, Pitt School of Medicine, and published online in *PLOS Genetics*, showed that nine variants in the gene associated with cystic fibrosis can lead to pancreatitis, sinusitis, and male infertility, but leave the lungs unharmed.

People with CF inherit from each parent a severely mutated copy of a gene called CFTR, which makes a protein that forms a channel for the movement of chloride molecules in and out of cells that produce sweat, mucus, tears, semen, and digestive enzymes, said Dr. Whitcomb. Without functional CFTR channels, secretions become thick and sticky, causing problems such as the chronic lung congestion associated with CF.

"There are other kinds of mutations of CFTR, but these were deemed to be harmless because they didn't cause lung problems," Dr. Whitcomb said. "We examined whether these variants could be related to disorders of the pancreas and other organs that use CFTR channels."

Co-senior author Min Goo Lee, M.D., Ph.D., of Yonsei University College of Medicine in Seoul, Korea, conducted careful tests of CFTR in pancreatic cell models and determined that a molecular switch inside the cell called WINK1 made CFTR channels secrete bicarbonate rather than chloride molecules.

"Pancreas cells use CFTR to secrete bicarbonate to neutralize gastric acids," Dr. Whitcomb said. "When that doesn't happen, the acids cause the inflammation, cyst formation, and scarring of severe pancreatitis."

The research team found nine CFTR gene variants associated with pancreatitis after testing nearly 1,000 patients with the disease and a comparable number of healthy volunteers. They also learned that each variant could impair the WINK1 switch to prevent CFTR from becoming a bicarbonate-secreting channel.

Co-senior author McGowan Institute for Regenerative Medicine affiliated faculty member Ivet Bahar, Ph.D., Distinguished Professor and John K. Vries Chair of Computational Biology, Pitt

School of Medicine, built a computer model of the CFTR protein's structure and determined that all the nine variants alter the area that forms the bicarbonate transport channel, thus impairing secretion of the molecule.

"It turns out that CFTR-mediated bicarbonate transport is critical to thin mucus in the sinuses and for proper sperm function," Dr. Whitcomb said. "When we surveyed pancreatitis patients, there was a subset who said they had problems with chronic sinusitis. Of men over 30 who said they had tried to have children and were infertile, nearly all had one of these nine CFTR mutations."

He added that identification of the mechanisms that cause the conditions make it possible to develop treatments, as well as to launch trials to determine if medications that are used by CF patients might have some benefit for those who do not have lung disease, but who carry the other mutations.

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Pittsburgh Post-Gazette

Pittsburgh Tribune-Review

Abstract (Mechanisms of CFTR functional variants that impair regulated bicarbonate permeation and increase risk for pancreatitis but not for cystic fibrosis. Jessica LaRusch, Jinsei Jung, Ignacio J. General, Michele D. Lewis, Hyun Woo Park, Randall E. Brand, Andres Gelrud, Michelle A. Anderson, Peter A. Banks, Darwin Conwell, Christopher Lawrence, Joseph Romagnuolo, John Baillie, Samer Alkaade, Gregory Cote, Timothy B. Gardner, Stephen T. Amann, Adam Slivka, Bimaljit Sandhu, Amy Aloe, Michelle L. Kienholz, Dhiraj Yadav, M. Michael Barmada, Ivet Bahar, Min Goo Lee, David C. Whitcomb. PLOS Genetics, published online 07/17/14.)

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