Key component in protein that causes cystic fibrosis identified

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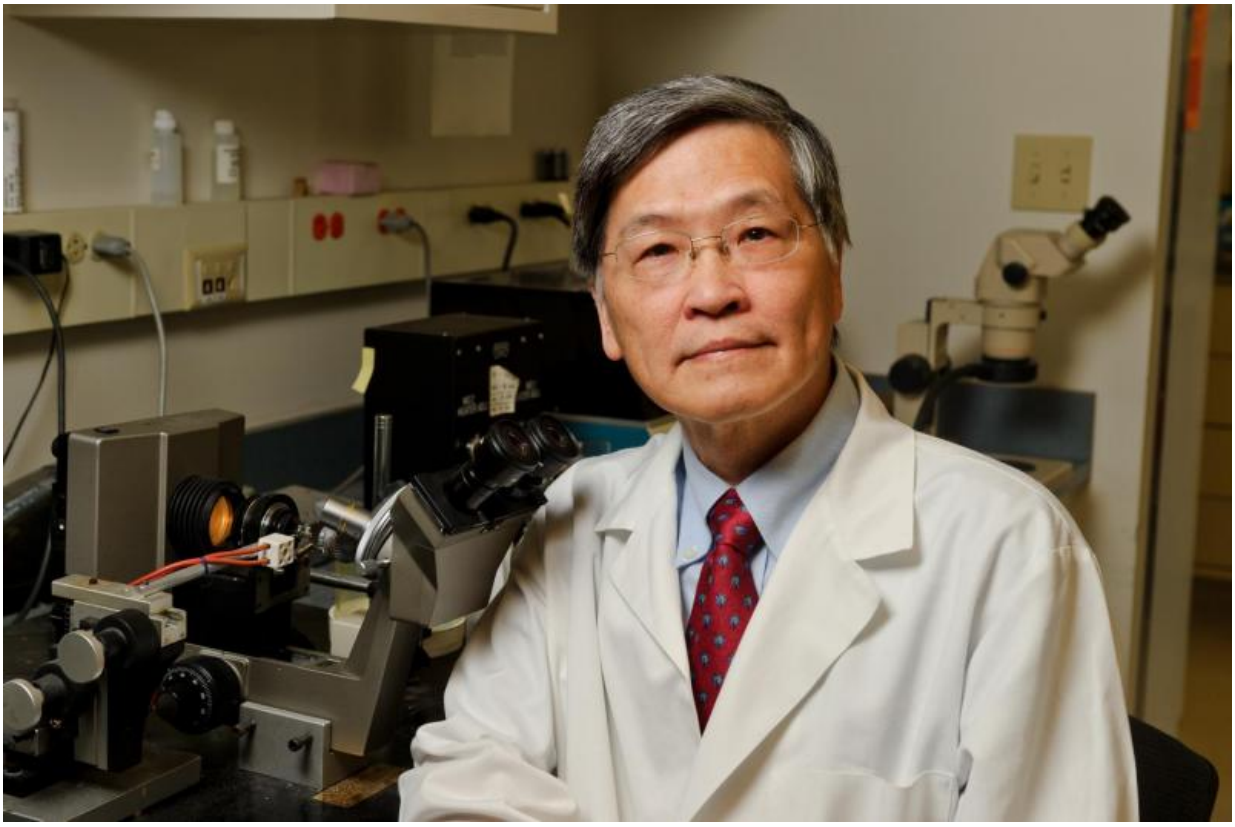


Researchers from the University of Missouri, led by Tzyh-Chang Hwang, Ph.D., have identified a key component in the protein that causes cystic fibrosis. It is a finding that may lay the foundation for the development of new medications and improved therapies. Credit: Justin Kelley/MU Health System

Nearly 70,000 people worldwide are living with cystic fibrosis, a life-

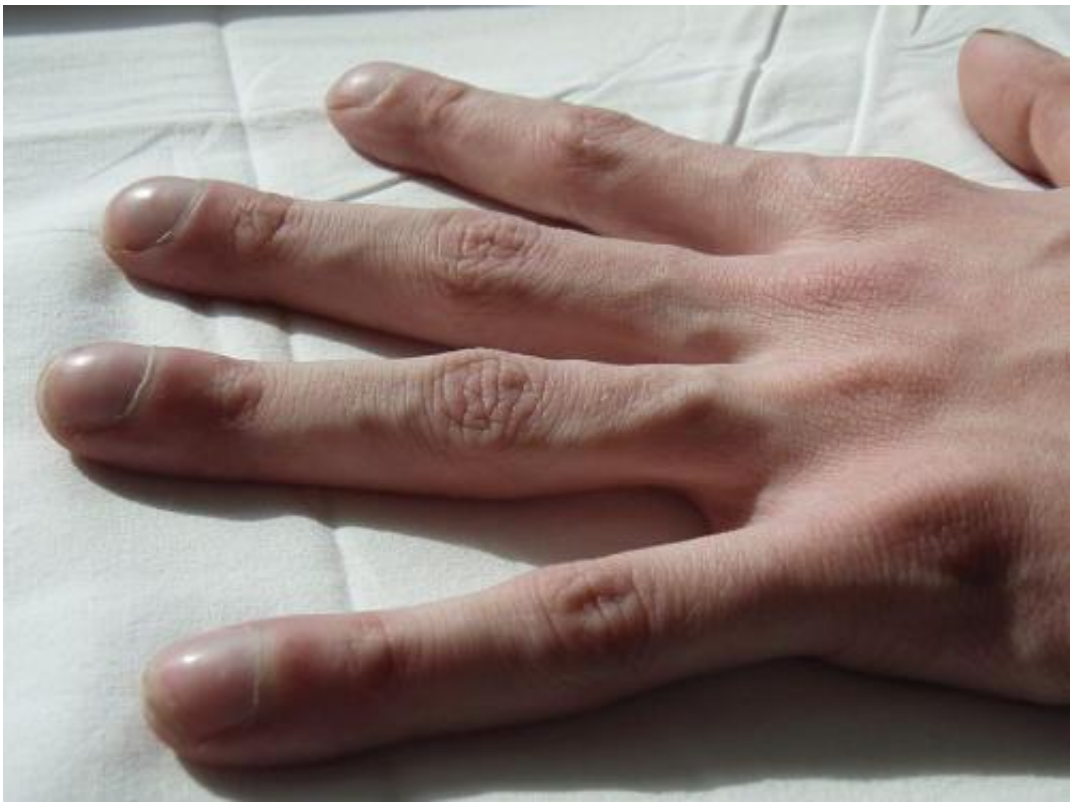
threatening genetic disease. There currently is no cure for the condition, but researchers from the University of Missouri have identified a key component in the protein that causes the disease. It is a finding that may lay the foundation for the development of new medications and improved therapies.

"We know that cystic fibrosis is caused by mutations in a gene called CFTR, but we don't know exactly how these mutations affect the function of the CFTR protein," said Tzyh-Chang Hwang, Ph.D., professor of medical pharmacology and physiology at the MU School of Medicine and lead author of the study. "In fact, there are nearly 2,000 mutations that could occur in the protein. However, our study identified two amino acids in the CFTR protein that serve as a sort of gate. This gate is a key factor in regulating the flow of chloride ions—one of the key ingredients in salt—into and out of the cells through the CFTR protein."

People with cystic fibrosis have an imbalance of salt in their bodies caused by the defective CFTR protein. Because there is too little salt and water on the outside of the cells, the thin layer of mucus that helps keep the lungs free of bacteria becomes very thick and difficult to expel by coughing. This thick mucus can clog the airways and lead to dangerous infections. Although advances in the understanding and treatment of the condition have allowed many people with the disease to live into their early 40s, the majority of patients with cystic fibrosis die of respiratory failure.

"In many ways, the function of the CFTR protein can be compared to a motion-activated water faucet," Hwang said. "All of the parts need to be functioning properly in order for the faucet to work. The motion sensor needs to detect your hand movements and send a signal to open the gate, enabling the flow of water. When the gate in the CFTR protein is defective, the flow of ions across the cell membrane is disrupted. By

identifying the amino acids that make up this gate, we now have a clear idea as to why a mutation in either of these two amino acids causes cystic fibrosis."



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

For decades, therapies for cystic fibrosis worked to maximize organ function and stave off organ failure, but did not address the root causes of the disease. However, in 2012, the U.S. Food and Drug Administration approved the drug, ivacaftor, to treat the underlying cause of cystic fibrosis in individuals with a specific mutation. While the drug targets the defective protein, the actual ways by which it enhances CFTR function are largely unknown. Hwang's previous research has shown how the drug affects the CFTR protein's gate, and his latest study

builds upon that knowledge by identifying the exact location of the gate. This allows Hwang and his team to further understand not only how the drug works, but also could shed light on where the drug works and therefore potentially improve upon its effects.

"When your water faucet is broken, you can call a plumber to repair it," Hwang said. "But if the plumber doesn't understand how the faucet works, how is he supposed to fix it? By understanding the physical and chemical basis of CFTR function, we, the molecular plumbers, are equipped with the tools to find ways to correct the defective protein's function, and subsequently boost treatments and ultimately improve the lives of cystic fibrosis patients."

More information: The study, "Localizing a Gate in CFTR," recently was published in *PNAS*. DOI: 10.1073/pnas.1420676112

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