

New genetic cause of pulmonary hypertension identified

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Columbia University Medical Center (CUMC) scientists have identified new genetic mutations that can cause pulmonary arterial hypertension (PAH), a rare fatal disease characterized by high blood pressure in the lungs. The mutations, found in the gene *KCNK3*, appear to affect potassium channels in the pulmonary artery, a mechanism not previously linked to the condition. Cell culture studies showed that the mutations' effects could be reversed with a drug compound known as a phospholipase inhibitor. The study was published today in the online edition of the *New England Journal of Medicine*.

"The most exciting thing about our study is not that we've identified a new gene involved in [pulmonary hypertension](#), but that we've found a drug that can 'rescue' some mutations," said co-senior author Wendy K. Chung, MD, PhD, associate professor of pediatrics and medicine at CUMC. "In genetics, it's common to identify a gene that is the source of a disease. However, it's relatively rare to find potential treatments for [genetic diseases](#)."

PAH is a progressive disorder characterized by abnormally high blood pressure in the [pulmonary artery](#), which reduces blood flow from the right side of the heart to the lungs. The heart can compensate by pumping harder, but over time this can weaken the heart muscle and lead to right-sided heart failure. Common symptoms of PAH include shortness of breath, dizziness, and fainting. About 1,000 new cases are diagnosed in the United States each year. The disorder is twice as common in females as in males. There is no cure for PAH and few

effective treatments. Most patients with PAH die within 5–7 years of diagnosis.

Some cases of PAH are caused by inherited genetic defects. Most of these "familial" cases have been linked to mutations in a gene called [BMP2](#) ([bone morphogenetic protein](#) receptor, type II), which was identified simultaneously in 2000 by two independent research teams, one led by the late Robin Barst and Jane Morse, CUMC researchers. However, the majority of cases are idiopathic in origin (of unknown cause). Other forms of PAH can be triggered by autoimmune diseases, congenital heart defects, infections (such as schistosomiasis), and medications (such as the now-banned diet-drug combination commonly known as fen-Phen).

Dr. Chung and her colleagues discovered the new mutations by sequencing the exomes (the portion of the genome that codes information to make proteins) of families with PAH without identified mutations. [KCNK3](#) mutations were found in 3.2 percent of those with familial disease and in 1.3 percent of those with idiopathic PAH.

The team found that the mutations alter the function of [potassium channels](#) by reducing the activity of these channels. Potassium channels help maintain the vascular tone of the pulmonary artery and help it respond to low levels of oxygen.

"We were surprised to learn that [KCNK3](#) appears to play a role in the function of potassium channels in the pulmonary artery," said Dr. Chung. "No one had suspected that this mechanism might be associated with PAH." The other gene linked to the disorder, [BMP2](#), is thought to cause PAH by ultimately promoting growth and multiplication of smooth muscle cells in the pulmonary artery, thereby restricting blood flow.

Dr. Chung also found, working in collaboration with co-senior author,

Robert S. Kass, PhD, the Alumni and David Hosack Professor of Pharmacology, chair of the department, and vice dean for research at CUMC, that the effects of the KCNK3 mutations could be reversed with an experimental phospholipase inhibitor called ONO-RS-082. The findings were made in cell cultures. Further study is needed to determine whether treatment with this or other drugs that affect potassium channels might be useful in the treatment of people with PAH, said Dr. Chung.

"KCNK3 [mutations](#) are a rare cause of PAH, so I don't want to oversell our findings," said Dr. Chung. "Still, it's exciting that we've found a mechanism that can lead to the disease that is a new, druggable target. It's also possible that targeting KCNK3 may be beneficial for patients who have PAH independent of their KCNK3 genetic status."

Provided by Columbia University Medical Center

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