Researchers discover genetic mutations that cause rare and deadly lung disease

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A team of researchers, led by physicians and scientists at Intermountain Healthcare's Intermountain Medical Center and ARUP Laboratories, has made a medical breakthrough by discovering genetic mutations that cause a rare and deadly lung disease.

The disease, pulmonary capillary hemangiomatosis or PCH, is a rare cause of pulmonary hypertension, which occurs predominantly in young adults. PCH affects less than one in a million people, and has been extremely difficult and expensive to diagnose, as well as challenging to treat.

This genetic discovery offers new hope.

"This is a significant finding. This discovery should advance our understanding of this rare pulmonary vascular disorder and other related disorders," said Greg Elliott, MD, MACP, senior investigator of the study and medical director of the Pulmonary Hypertension Center at Intermountain Medical Center in Murray, Utah, and professor of medicine at the University of Utah School of Medicine.

Results of the study will be published in the February issue of the journal *Chest*, the official publication of the American College of Chest Physicians.

Dr. Elliott and his team at Intermountain Medical Center and the University of Utah School of Medicine collaborated with researchers

from Columbia University, Vanderbilt University and Mayo Clinic-Scottsdale.

To find the genetic mutation, the research team used a relatively new technology – whole exome sequencing – performed at ARUP Laboratories in Salt Lake City to test DNA samples. They discovered the genetic mutations in Eukaryotic Translation Initiation Factor 2 Alpha Kinase 4. EIF2AK4 is a protein responsible for down-regulating protein synthesis when cells are exposed to stress.

Researchers found that in patients with the genetic mutations, their bodies don't properly regulate blood vessels in the lung. As a result, the capillaries in the lungs proliferate and the patient develops pulmonary hypertension.

D. Hunter Best, PhD, and Kelli L. Sumner, BS, two scientists on the research team, conducted the exome sequencing and analyzed the data in collaboration with colleagues at Columbia University and Vanderbilt University.

"Whole exome sequencing is breakthrough technology that allows us to test accurately and cost effectively for rare genetic disorders," said Dr. Elliott. "Without Dr. Best's expertise and the work done by Kelly Sumner in the laboratory, this discovery would not have occurred."

For those who receive a diagnosis of PCH, it becomes a life-changing event, where risky, expensive treatments are used to slow the progression of the deadly disease.

It's also difficult to diagnose, often delaying proper treatment. Without a correct diagnosis, physicians may try ineffective and costly therapies because PCH's symptoms resemble many other lung diseases.

Dr. Elliott says the discovery of the genetic cause of PCH should allow the correct diagnosis to be made earlier.

"This disease is not easily treated," he added. "Most therapies are expensive and probably misapplied – or their value is limited. They also can pose significant risks to the patient. Accurate early diagnosis and treatment based upon a correct diagnosis should bring increased value to patients and their families."

With the finding, physicians can now choose to order a genetic test to help diagnose the disease. Previously, patients with findings that suggested PCH sometimes underwent a lung biopsy to seek an accurate diagnosis. In some cases this was either too risky to do, or the patient experienced complications following the biopsy.

"Now we can test for disease-causing mutations in EIF2AK4, and correctly diagnose PCH or related conditions," said Dr. Elliott. "A correct diagnosis allows us to design the best treatment plan possible, save patients the added cost of ineffective therapies and unnecessary interventions – and most importantly, save lives."

Discovery of the gene mutations should also allow scientists to study the paths to disease development and to look for new ways to treat patients. Scientists can turn off (knock out) the gene in animal models to discover how the disease develops. Investigators also can explore targeted gene therapy or the effects of drugs that modify the function of the mutated gene.

"My hope is to ultimately find a treatment for this disorder and for the people affected with PCH and diseases like it. As their doctor, I see the suffering and I want to help," said Dr. Elliott.

Provided by Intermountain Medical Center