Inherited genetic cause, possible treatment found for complex lung disorder

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A tale of two sisters has helped researchers solve a medical mystery and discover a familial genetic mutation that causes an inherited form of the lung disease Pulmonary Alveolar Proteinosis (PAP).

Reporting their results in the Nov. 24 *Journal of Experimental Medicine*, a research team led by Cincinnati Children's Hospital Medical Center also points to the possibility of an inhaled therapy to overcome a chain of molecular events that lead to PAP. The lungs of people with PAP fill with pulmonary surfactant, a substance composed of lipids (fats) and proteins, causing labored breathing and respiratory failure. Surfactant's normal role is to coat lung tissues and keep the lungs from collapsing

Finding an effective, non-invasive therapy would dramatically improve quality of life for children and adults with PAP, said Bruce Trapnell, M.D., a physician/researcher in the division of Pulmonary Biology at Cincinnati Children's and the report's senior author.

"This is the first data to demonstrate familial PAP in humans and the critical role of the gene CSF2RA to balanced surfactant levels in the lung," Dr. Trapnell said. "These findings provide a basis for developing better forms of treatment that would be a major benefit to patients."

The current front-line treatment is whole-lung wash, where a tube is inserted into the airway under anesthesia to flush out the lungs.

People with PAP can also acquire secondary infections. This happens

when immune system cells in called macrophages and neutrophils, which ingest and destroy foreign matter, are deprived of the effects of GM-CSF. The lack of GM-CSF activity impairs the cells' ability to remove infectious organisms from the lungs.

The multi-institutional team studied the cases of two sisters, ages 6 and 8, whose PAP progressed slowly prior to diagnosis. For two years prior to diagnosis, the younger sister had suffered from labored breathing and had below average height and weight (third percentile) of unexplained origin.

The 8-year-old sister had been considered healthy until results for several novel disease biomarkers developed by Dr. Trapnell's team prompted doctors to examine her. She also was found to be below average height and weight for her age (10th percentile). The older sister also had blood and breathing test results consistent with PAP, including elevated blood levels of surfactant protein and an accumulation of surfactant in her lungs.

Researchers found a mutation of the CSF2RA gene in both sisters. The mutation disrupted the signaling activity of protein called GM-CSF, a cytokine that facilitates cellular communication and is critical for the body to control the right amount of surfactant production.

Under normal conditions, CSF2RA encodes a receptor for GM-CSF called GM-CSA-Ra. Without a normal receptor, GM-CSF doesn't bind and signal its activation targets properly and the lungs fill with surfactant.

Both parents are healthy and do not have PAP, but each carried different forms of the gene mutation that caused PAP in both children. The sisters' gene mutations were detected on maternal and paternal X chromosomes, the researchers said. Prompting them to check genetic

regulation of GM-CSF in the sisters were earlier studies in mice, conducted by researchers at Cincinnati Children's and others. Those previous studies indicated the malfunction of GM-CSF in binding to another receptor (GM-CSF-RB) inhibits GM-CSF signaling and causes PAP symptoms in mice.

In their current report, researchers suggest an inhaled GM-CSF aerosol could boost the activity of the GM-CSF receptor in patients to correct surfactant levels. They also point to the possibility of bone marrow transplant and gene therapy as other alternatives. The multi-institutional research team plans to move forward with studies of these potential treatments, said Dr. Trapnell, also professor of Medicine and Pediatrics at the University of Cincinnati College of Medicine.

Both sisters, who are not identified in the report, would be included in any trials involving new therapy, Dr. Trapnell added. The younger sister has undergone whole-lung lavage treatment at Cincinnati Children's. This improved her condition, although the invasive treatment may require repeated procedures.

There have been PAP cases where patients do not exhibit obvious symptoms, according to the Pulmonary Alveolar Proteinosis Foundation. The researchers in this report were intrigued by the slow onset of PAP observed in both sisters, especially the older sibling originally thought to be healthy. They concluded that despite the genetic mutation, higher than normal levels of GM-CSF in the girls may have partially rescued its cellular signaling enough to slow the development of PAP.

Source: Cincinnati Children's Hospital Medical Center