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Gene mutation may reveal clues for treating lung diseases

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(PhysOrg.com) -- A genetic mutation found in four children born with multiple abnormalities may provide insight into potential treatments for newborn lung distress and chronic obstructive pulmonary disease (COPD).

The children were born with abnormally developed lungs, gastrointestinal and urinary systems, skin, skull, bones and muscles. In addition, all had cutis laxa, an inherited connective tissue disorder that causes skin to hang loosely from the body. Three of the patients died from respiratory failure before age 2.

Details about the discovery of the mutation, found by researchers from Washington University School of Medicine in St. Louis, McGill University, New York University Langone Medical Center and collaborating institutions, are published in the Oct. 15 online edition of the American Journal of Human Genetics.

Elaine C. Davis, Ph.D., senior author and associate professor of anatomy and cell biology at McGill University in Montreal, Canada, compared various tissues from a mouse genetically engineered to be missing a form of the LTBP4 gene with skin tissue samples from one of the children. She found remarkable similarities. The mouse, provided by Daniel Rifkin, M.D., the Charles Aden Poindexter Professor of Medicine and professor of cell biology at NYU Langone Medical Center, showed similar connective tissue alterations by electron microscopy as the patient. The child had cutis laxa, lethal pulmonary complications and

gastrointestinal and urinary disease.

Based on these observations, researchers in the laboratory of Zsolt Urban, Ph.D., a pediatric geneticist at Washington University School of Medicine, sequenced the LTBP4 gene in the four children and confirmed they had mutations. He determined that the patients were the first described to show severe symptoms of a novel syndrome, which the researchers have named Urban-Rifkin-Davis Syndrome.

The findings have potential implications for newborns with underdeveloped lungs as well as older patients with severe lung diseases, including COPD, says Urban, first author of the paper.

"Many newborns commonly have breathing difficulties," Urban says. "Part of the problem is that the lung is not developed properly, especially the alveoli, the tiny sacs at the end of the smallest airways that serve as a place for oxygen uptake and gas exchange. This finding helped us identify a gene essential for the development of alveoli and potentially provide a target for intervention in premature babies."

Urban says potential treatments could include introducing the protein product of the LTBP4 gene to the newborn or using existing drugs that can moderate transforming growth factor beta (TGFß), which is overactivated in the tissues of these children. The drug losartan, now in trials for treating Marfan syndrome, another connective tissue disorder, has been shown to limit TGFß and merits further research as a possible treatment.

The researchers now are broadening their research into the new syndrome among other patients with cutis laxa. Urban, assistant professor of pediatrics, of medicine and of genetics at Washington University School of Medicine, heads the International Center for the Study of Cutis Laxa at St. Louis Children's Hospital.

"We are finding that about 70 percent of cutis laxa patients with pulmonary, gastrointestinal and urinary problems have Urban-Rifkin-Davis Syndrome," Urban says. "Now we will look at what percentage of cutis laxa patients with only pulmonary problems have the mutation."

Early developmental problems that are not detectable in childhood may predispose a person to age-related disease such as COPD, Urban says. Urban and colleagues are also testing samples collected from patients with COPD for LTBP4 mutations. When lungs are damaged with COPD, alveoli lose their elastic quality, and the walls between them are destroyed as they become thick and inflamed.

"Patients who may have a slightly reduced activity of LTBP4 might be more susceptible to chronic lung diseases later in life," Urban says. "Identifying genes that are central for the formation of alveoli may help us devise ways to regenerate alveoli in patients with COPD."

More information: Urban Z, Hucthagowder V, Schürmann N, Todorovic V, Zilberberg L, Chio J, Sens C, Brown C, Clark R, Holland K, Marble M, Sakai L, Dabovic B, Rifkin D, Davis EC. Mutations in LTBP4 cause a syndrome of impaired pulmonary, gastrointestinal, genitourinary, musculoskeletal and dermal development. *American Journal of Human Genetics.* Advance online publication Oct. 15, 2009.

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