Mutations in two genes linked to familial pulmonary fibrosis and telomere shortening

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Dr. Christine Kim Garcia, Associate Professor of Internal Medicine and with the Eugene McDermott Center for Human Growth and Development. Credit: UT Southwestern Medical Center

Researchers at UT Southwestern Medical Center have identified mutations in two genes that cause a fatal lung scarring disease known as familial pulmonary fibrosis.

Researchers also determined that these mutations cause excessive shortening of the ends of chromosomes, known as telomeres. Telomeres are repetitive sequences of DNA that protect the ends of chromosomes from deteriorating. They are sometimes compared to the plastic ends of shoelaces, which protect shoelaces from fraying.

Together, these genes—PARN and RTEL1—explain about 7 percent of familial pulmonary fibrosis and strengthen the link between lung fibrosis and telomere dysfunction, according to the study, done in conjunction with the Yale Center for Genome Analysis, and which appears online in *Nature Genetics*.

"Although RTEL1 had been previously linked to telomere biology, our finding that PARN was involved in telomere regulation and human disease was completely unexpected," said senior author Dr. Christine Kim Garcia, Associate Professor of Internal Medicine and with the Eugene McDermott Center for Human Growth and Development.

About 50,000 people in the United States annually develop idiopathic pulmonary fibrosis, a progressive disease that principally affects the elderly, according to the Pulmonary Fibrosis Foundation. Approximately one in 20 people have a close relative with the disease, in which case they are considered to have familial pulmonary fibrosis. Without a lung transplant, pulmonary fibrosis patients typically die within three years after diagnosis.

The genetic research was made possible by UT Southwestern's highly active lung transplant program, said Dr. Garcia, who holds the Kern and Marnie Wildenthal President's Research Council Professorship in

Medical Science.

"My clinical colleagues are attuned to asking patients about their family history and letting patients know that we have an active research program investigating the inherited form of this disease," said Dr. Garcia, whose lab focuses on defining the genetic underpinnings of adult-onset lung disease.

The research team identified 99 families that had the inherited form of the disease, but did not have mutations in one of the previously identified genes. Using a technique known as exome sequencing, the researchers identified mutations in PARN and RTEL1 in 12 percent of these families.

"There were statistically more mutations found in these two genes than you would expect by chance," Dr. Garcia said.

The researchers used a biological assay technique called quantitative PCR (or real-time polymerase chain reaction) to measure telomere lengths in these patients.

"We found that the mean, age-adjusted telomere length of all rare variant carriers was significantly shorter than normal controls," said the study's first author, Dr. Bridget Stuart, Assistant Professor of Pediatrics and with the Eugene McDermott Center for Human Growth and Development. "This finding implicates both genes in telomere maintenance as well as development of pulmonary fibrosis."

The new findings add to previous research led by Dr. Garcia that had identified mutations in three other genes as being linked to familial pulmonary fibrosis. Two of those genes, TERT and TERC, like PARN and RTEL1, affect telomere length. The third, SFTPA2, affects a protein expressed only in the fluid that bathes the lung's epithelial cells.

Altogether, mutations in the five identified genes account for about 25 percent of all cases of familial pulmonary fibrosis.

"Our ultimate goal is to gain a full understanding of what causes the genetic form of this disease so that effective medications can be developed," Dr. Garcia said.

More information: Exome sequencing links mutations in PARN and RTEL1 with familial pulmonary fibrosis and telomere shortening, DOI: 10.1038/ng.3278

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