Researchers identify gene linked to inherited form of fatal lung disease

19 December 2008

Researchers at UT Southwestern Medical Center have determined that a mutation in a gene known for its role in defending the lungs against invading pathogens is responsible for some inherited cases of a lethal lung disease affecting older adults. The same mutation may also be associated with lung cancer, the researchers said.

This is the third gene that UT Southwestern scientists have linked with idiopathic pulmonary fibrosis, or IPF. The study appears online this week and in the January issue of *American Journal of Human Genetics.*

In the U.S., about 200,000 patients have IPF, and about 40,000 patients die from the disease each year, according to the Pulmonary Fibrosis Foundation. The disease typically strikes people in their 50s and older, causing severe scarring of the lungs. Death usually occurs within three years of diagnosis.

"We don't have any medicines to treat this disease," said Dr. Christine Garcia, assistant professor in the Eugene McDermott Center for Human Growth and Development and of internal medicine at UT Southwestern and the study's senior author. "If a patient is younger than 65, lung transplantation is an option, but most people who develop IPF are older than that."

The ultimate goal, Dr. Garcia said, is to find or develop a medication that can stem the progression of this pulmonary condition.

About one in 50 IPF patients have an inherited form of the disease. It is this familial form of the disease that Dr. Garcia her colleagues are focused on.

"We've been trying to identify the genes and genetic variants that underlie this disease," Dr. Garcia said. "Now, we know there are multiple genes involved."

In 2007, Dr. Garcia and her research team studied two large families in which multiple individuals were affected with IPF to search for a gene causing the disease. This led to the discovery of mutations in genes called TERT and TERC. These two genes are normally responsible for producing the telomerase enzyme, which elongates the lengths of DNA at the ends of chromosomes, called telomeres. In normal cells, telomeres shorten each time the cell divides. When they reach a certain length, the cell stops dividing. In most cancerous cells, telomeres don't shorten during cell division, allowing the cells to remain effectively immortal. Mutations in either of these two genes can be found in almost 15 percent of those with familial IPF. Up to 40 percent have short telomere lengths and evidence of telomerase dysfunction.

"But we were still left with a big question mark," Dr. Garcia said. "What about the rest of the families that have normal telomere lengths? What was causing their lung disease?"

In the current study, Dr. Garcia and her team focused on families that did not have TERC or TERT mutations. By using a genomic linkage approach – a technique that scans the entire human genome for regions of DNA that are shared in common by all the individuals with the disease – they were led to mutations in a gene called SFTPA2. The protein produced by this gene, surfactant protein A2, is found in the fluid of the lungs and helps protect the organ from invading pathogens.

Many of the individuals in this family who carried this mutation had not only IPF but also lung cancer, especially adenocarcinoma, with features of bronchioloalveolar cell carcinoma. It is known that people with IPF have a higher risk for developing lung cancer, and Dr. Garcia suspects that mutations in the SFTPA2 gene are associated with both IPF and lung cancer. Another family harboring a different mutation in the SFTPA2 gene also had

members that exhibited IPF and lung cancer.

Dr. Garcia and her team are now working on molecular studies in cells to determine why these gene mutations put patients at risk for either of these diseases. They are also working to develop an animal model in order to determine the specific effects of SFTPA2 on different cells in the lungs.

Source: UT Southwestern Medical Center