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Researchers map potential genetic origins, pathways of lung cancer in nonsmokers

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Researchers at the Translational Genomics Research Institute (TGen) have begun to identify mutations and cellular pathway changes that lead to lung cancer in never-smokers -- a first step in developing potential therapeutic targets.

"This is the starting point. We certainly have a lot of pathways and gene expression alterations that we're going to be very interested in confirming and looking at in larger cohorts of patients," said Dr. Timothy G. Whitsett, Senior Postdoctoral Fellow in TGen's Cancer and Cell Biology Division.

Whitsett presented the findings today at the American Association for Cancer Research (AACR) and International Association for the Study of Lung Cancer (IASLC) Joint Conference on Molecular Origins of Lung Cancer: Biology, Therapy and Personalized Medicine, held Jan. 8-11, 2012, at the San Diego Marriott Marina & Hotel.

"This is a very important subset of patients with lung cancer, and our research looks to identify pathways and genes that are potentially driving this cancer," said Dr. Whitsett, who works under Dr. Nhan Tran, head of TGen's CNS Tumor Research Lab. The title of the abstract Dr. Whitsett presented is Identification of key tumorigenic pathways in never-smoker lung adenocarcinoma patients using massively parallel DNA and RNA sequencing.

Never-smokers are defined for this study as individuals who smoked less

than 100 cigarettes in their lifetime. About 10 percent of lung cancer cases occur in this patient population, which researchers have not examined as extensively as they have studied patients with lung cancer who smoked.

Whitsett and his colleagues looked at three female patients with adenocarcinoma: one never-smoker with early-stage disease; one never-smoker with late-stage disease; and, as a comparison, one smoker with early-stage disease. The team performed whole genome sequencing (WGS) and whole transcriptome sequencing (WTS) on each patient to identify gene mutations and pathway alterations that could have led to the development and progression of their specific lung cancer.

"In the never-smoker with early-stage cancer, there are very few mutations in the genome, but when we looked at the whole transcriptome, we see differences in gene expression," Whitsett said.

In the never-smoker with late-stage disease, researchers found mutations in what Whitsett called "classic tumor-suppressor genes." He and his colleagues hypothesize that mutations of the tumor-suppressor genes might be a factor in late-stage lung cancer in never-smokers.

Notably, the researchers reported that these never-smokers' tumors lacked alterations in common genes associated with lung cancer such as EGFR, KRAS and EML/ALK translocations. This finding makes these patients ideal cases for the discovery of new mutations that may drive lung adenocarcinomas in never-smokers, according to the researchers.

Whitsett said that using WGS and WTS to identify cancer origins "has become a way to really dive down into an individual tumor to try to understand the pathways that may be driving that tumor and identify what therapeutic interventions may be possible."

The researchers are now validating these findings in about 30 never-smokers with lung adenocarcinoma and about 60 clinically matched smokers with lung adenocarcinoma.

Provided by The Translational Genomics Research Institute