

TCGA discovers potential therapeutic targets for lung squamous cell carcinoma

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Changes in DNA that are important to the initiation and progression of lung cancer also identified by NIH-supported researchers

Researchers have identified potential therapeutic targets in lung squamous cell carcinoma, the second most common form of lung cancer. The Cancer Genome Atlas (TCGA) Research Network study that appeared online Sept. 9, 2012, and in print Sept. 27, 2012, in the journal *Nature*, comprehensively characterized the lung squamous cell carcinoma genome. The study found a large number and variety of DNA alterations, many of which seem to be driving forces behind pathways that are important to the initiation and progression of lung cancer. TCGA is jointly funded and managed by the National Human Genome Research Institute (NHGRI) and the National Cancer Institute (NCI), both part of the National Institutes of Health.

“With these findings, TCGA researchers have set the stage for the development, testing and implementation of advanced diagnostics and therapeutics for lung squamous cell carcinoma,” said NIH Director Francis S. Collins, MD, PhD. “These findings also underscore the power and value of our nation’s investment in The Cancer Genome Atlas.”

Researchers have made important strides in understanding and developing precision medicine treatments for adenocarcinomas, which are the most common type of lung cancer. But these treatments have been largely ineffective in treating lung squamous cell carcinoma. Lung squamous cell carcinoma frequently develops in the large airways in the center of the lungs, while adenocarcinomas often arise at the edges of the lungs. Lung adenocarcinomas sometimes affect non-smokers, while lung squamous cell carcinomas arise almost exclusively in smokers.

“This report provides an unprecedented view of the spectrum and high rate of genomic mutations that are found in lung squamous cell carcinoma,” said Eric D. Green, MD, PhD, NHGRI director. “We hope this report will spur basic research to better understand the genesis of the disease, and in clinical research as these new findings are factored into potential treatment approaches.”

In this study, researchers identified promising therapeutic targets, including three families of tyrosine kinases, which are enzymes that function as on or off switches in many cellular functions and are frequently mutated in cancer. These enzymes were found to be mutated or amplified in many of the tumors analyzed by TCGA investigators. Importantly, enzymes in these families have been established as potential therapeutic targets in pre-clinical studies and investigated clinically as therapeutic targets in other cancer types. In an ancillary finding, in 69 percent of the tumors studied, investigators detected gene alterations in important signaling pathways that could also serve as therapeutic targets.

“Genomic analysis of lung adenocarcinomas has led to many important therapeutic advances and this new research helps to explain why squamous lung cancers have not been responsive to drugs that work for adenocarcinomas,” said Harold Varmus, MD, director, NCI. “Because the spectrum of mutations is very different in each type, the identification of these new mutations by TCGA researchers has the potential to lead to therapeutic advances for squamous lung cancers.”

For this study, researchers examined tissue samples from 178 patients with untreated lung squamous cell carcinomas. Notably, 96 percent of the patients in this study had a history of tobacco use. Researchers compared the tumor genome to the genome in normal tissue to make sure that a change in the tumor genome was the result of a mutation. The carcinomas

exhibited a large number and variety of alterations, many of which appeared to deleteriously affect pathways that are important to the initiation and progression of cancer. Genes that help detoxify cells and repair damage, or are involved in cell specialization, were frequently altered.

Researchers also sequenced the whole genomes of 19 tumor and normal tissue pairs to gather comprehensive information about genomic rearrangements. This is the first TCGA report to describe whole genome sequencing, which allows researchers to map the variety of changes that can occur in a tumor's genome, including the breaking and rejoining of chromosomes and other large structural alterations that might be involved in the genesis of the disease. These whole genome data will be freely available for future in-depth analysis that could help locate mutations in intergenic regions, which are stretches of DNA sequences

located between clusters of genes that may not encode proteins but sometimes control nearby genes.

Researchers found alterations of the TP53 gene in 90 percent of the tumors and inactivation of the CDKN2A gene in 72 percent of tumors. In their non-mutated or unaltered state, both genes function as tumor suppressors to prevent cancer. When they are altered, however, cancer is able to grow unconstrained. Researchers also identified previously unreported mutations that reduce the function of the HLA-A gene in the tumors. HLA controls how the immune system distinguishes the body's own cells from foreign invaders.

Researchers speculate that mutations in the HLA gene may help the tumor escape the body's regular surveillance of mutated cells. Involvement of the HLA-A gene suggests that treatment strategies for some patients using customized immunotherapies could be effective. Recent clinical trials suggest that new biological agents, which work by decreasing the immune response and allow the immune system to react against cancer cells, may be effective treatments for some lung cancer patients.

"These TCGA findings should stimulate a wide variety of new clinical trials for patients with squamous cell lung cancer and specific genotypic alterations," said Matthew Meyerson, MD, PhD, of the Dana-Farber Cancer Institute, the Broad Institute and Harvard Medical School, who co-led the project within TCGA. "These will include clinical trials of PI3 kinase inhibitors and other tyrosine kinase inhibitors, as well as ways to use genomics to select patients for trials of lung cancer treatments that dial down the immune response."

So far, The Cancer Genome Atlas Research Network has published analyses on these cancers:

- glioblastoma multiforme (http://cancergenome.nih.gov/newsevents/newsannouncements/news_9_4_2008)
- ovarian serous adenocarcinoma (<http://cancergenome.nih.gov/newsevents/newsannouncements/ovarianpaper>)
- colorectal adenocarcinoma (<http://www.cancer.gov/newscenter/pressreleases/2012/TCGacolorectal>)

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Participants in the TCGA Lung Squamous Cell Carcinoma Working Group: Face to Face Meeting at UNC

More details about The Cancer Genome Atlas, including Quick Facts, Q&A, graphics, glossary, a brief guide to genomics and a media library of available images can be found at <http://cancergenome.nih.gov>.

Reference: The Cancer Genome Atlas Research Network. Comprehensive genomic characterization of squamous cell lung cancers. *Nature*. Online Sept. 9, 2012, and in print Sept. 27, 2012. DOI:**10.1038/nature11404**.

NHGRI is one of the 27 institutes and centers at the National Institutes of Health, an agency of the Department of Health and Human Services. The NHGRI Division of Intramural Research develops and implements technology to understand, diagnose and treat genomic and genetic diseases. Additional information about NHGRI can be found at its website, <http://www.genome.gov>.

NCI leads the National Cancer Program and the NIH effort to dramatically reduce the burden of cancer and improve the lives of cancer patients and their families, through research into prevention and cancer biology, the development of new interventions, and the training and mentoring of new researchers. For more information about cancer, please visit the NCI website at <http://www.cancer.gov> or call NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237).

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