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Study identifies novel genomic changes in the most common type of lung cancer (Update)

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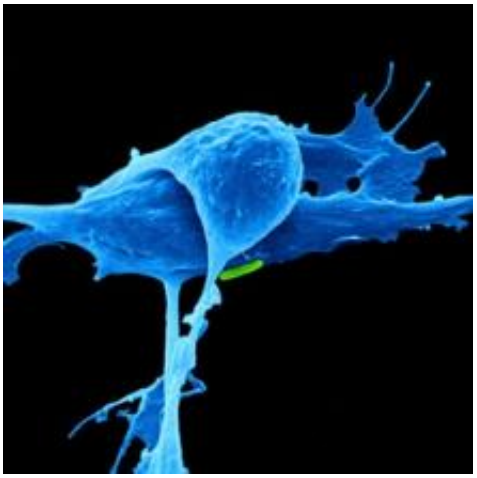

Researchers from The Cancer Genome Atlas (TCGA) Research Network have identified novel mutations in a well-known cancer-causing pathway in lung adenocarcinoma, the most common subtype of lung cancer. Knowledge of these genomic changes may expand the number of possible therapeutic targets for this disease and potentially identify a greater number of patients with treatable mutations because many potent cancer drugs that target these mutations already exist.

TCGA is jointly funded and managed by the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI), both part of the National Institutes of Health. A TCGA analysis of

another, less common, form of lung cancer, squamous cell carcinoma, was reported in 2012.

In this new study, published online July 9, 2014, in the journal *Nature*, researchers examined the genomes, RNA, and some protein from 230 lung adenocarcinoma samples. In three-quarters of the samples, the scientists ultimately identified mutations that put a cell signaling pathway known as the RTK/RAS/RAF pathway into overdrive.

"The integrated nature of TCGA analysis made these findings and their potential therapeutic implications possible," said NIH Director Francis S. Collins, M.D., Ph.D. "We hope this lays the groundwork for future work in precision medicine."

Mutations affecting the RTK/RAS/RAF pathway can cause it to become stuck in the "on" state. As a result, signals that promote cancer cell proliferation and survival are produced continuously. However, some drugs currently available curb aberrant activity of this pathway and prompt therapeutic responses in patients.

"Combined with the earlier TCGA analysis of squamous lung cancers, we now have a comprehensive understanding of many of the genetic pathways that lead to cancers of the lung," said NCI Director Harold Varmus, M.D. "Based on this knowledge, we can now seek better pathway inhibitors to improve patient outcomes. However, for the time being, stopping smoking or never starting remain the most reliable ways to reduce the number of deaths due to lung cancer."

In the group's initial scan of tumor samples, researchers identified gene mutations that would increase RTK/RAS/RAF pathway activity in 62 percent of the samples. The affected genes are oncogenes, or genes that have the potential to cause cancer when mutated or expressed at high levels. Consequently, these tumor samples were classified as oncogene-

positive.

To identify additional alterations, the investigators looked at DNA copy number changes, or changes in gene number resulting from the deletion or amplification (multiplication) of sections of DNA in the genome. In doing so, they detected amplification of two oncogenes, ERBB2 and MET, which are part of the RTK/RAS/RAF pathway. Gene amplification usually leads to increased expression of the encoded protein in cells.

Now that these amplifications have been identified, clinicians may be able to treat patients whose tumors have specific gene changes with drugs currently available or under development.

"It is quite striking that we have now identified an actionable mutation in over 75 percent of patients with lung adenocarcinoma, a significant improvement from a decade ago," said Matthew Meyerson, M.D., Ph.D., Harvard Medical School, Dana-Farber Cancer Institute, The Broad Institute, and one of the lead investigators on the project.

Additional analysis identified other genes that may play important roles in lung cancer development. Mutations in one of these genes, NF1, had previously been reported in lung cancer; NF1 is a known tumor suppressor gene that regulates the RTK/RAS/RAF pathway. Mutations in NF1 also put the pathway into overdrive. Another mutated gene, RIT1, is also part of the RTK/RAS/RAF pathway, and this is the first study to associate mutation of this gene with lung cancer.

"This most recent TCGA study again demonstrates the power, depth and breadth of TCGA data," said NHGRI Director Eric Green, M.D., Ph.D. "These results give us important new genomic insights into the development and behavior of an important form of cancer."

In the aggregate, the several forms of lung cancer comprise the most common cause of cancer-related deaths worldwide, with more than 1 million deaths annually. NCI estimates that only 17.5 percent of people diagnosed with lung cancer are still alive five years later.

Lung adenocarcinoma, the most common form of the disease in the United States, develops in tissues near the outer parts of the lungs and can spread widely. Although smoking is the main risk factor, adenocarcinoma is also the most common type of lung cancer among lifelong non-smokers and the risk of lung cancer is increased by 20 percent to 30 percent by exposure to secondhand smoke.

More information: Baylin SB, Govindan R, Meyerson M et al. for The Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. *Nature*. July 9, 2014. DOI: 10.1038/nature13385

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