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Recurrent but rare mutations might underlie cancer growth

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A potential new gene mutation that might drive lung cancer development and growth has been identified by researchers at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC-James).

A multi-institutional team led by OSUCCC-James researchers reports the findings in the *Journal of Clinical Investigation*. The study describes a patient with advanced lung cancer who was treated with the targeted drug sorafenib while on a clinical trial. Within two months, she demonstrated a near complete response, and she remained progression-free and asymptomic for five years while continuing to take sorafenib by mouth.

This patient was one of nine who responded to the treatment during the 306-patient trial, and had by far the best and longest lasting response to the drug. Unfortunately, only a few of these patients had tissues available for analysis.

The researchers used whole-genome sequencing to analyze for acquired mutations in genes in a sample of the patient's cancer cells prior to her use of sorafenib. They also sequenced RNA from the patient's tumor and healthy cells. These analyses were done to look for a possible genetic difference responsible for the sustained response to sorafenib. As is common in lung cancer, they found more than a hundred alterations in the structure of genes in this patients tumor compared to her normal cells—about a dozen of which were expressed at high levels—and one

was a plausible target for the drug sorafenib. This specific mutation (ARAF S214C) in the patient's cancer cells was both mutated and expressed at abnormally high levels. The researchers found additional ARAF mutations across 1 percent of an independent group of lung cancer cases. By engineering this mutation into normal lung cells, they showed that this abnormal gene formed tumors from these cells, and that these tumors were inhibited by the drug used in the patient.

"If recurrent but rare mutations underlie cancer growth and responsiveness, they are not likely to be statistically called out as a potential driver of cancer through a genome scan of several hundred or even thousands of cases because they are so rare. But for the patients who do have these specific genetic mutations, having this information is critical," says David Carbone, MD, senior and co-corresponding author of the study and director of The OSUCCC-James Thoracic Oncology Program.

"Our study suggests that we can discover important new gene mutations that drive cancer development and progression by analyzing genes in cancer cells from patients who fare far better or far worse than others in a particular clinical trial."

Carbone adds that using genome sequencing to identifying genetic mutations in a patient's cancer cells can help better match patients with drugs that are most likely to eradicate their cancer.

"Knowing which mutations are present in lung tumors can help us tailor a patient's treatment to the unique genetic features present in his or her cancer cells. That knowledge can also help us develop new drugs that target previously unrecognized gene mutations in lung and other cancers. This is a great example of new scientific discoveries being made from clinical observations in patients, which can then be brought back to the clinic to help future patients."

More information: "Oncogenic and sorafenib-sensitive ARAF mutations in lung adenocarcinoma." Marcin Imielinski, Heidi Greulich, Bethany Kaplan, Luiz Araujo, Joseph Amann, Leora Horn, Joan Schiller, Miguel A. Villalona-Calero, Matthew Meyerson, David P. Carbone *J Clin Invest.* 2014; DOI: 10.1172/JCI72763

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