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Study defines a new genetic subtype of lung cancer

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A report from investigators at the Massachusetts General Hospital (MGH) Cancer Center has defined the role of a recently identified gene abnormality in a deadly form of lung cancer. Tumors driven by rearrangements in the ROS1 gene represent 1 to 2 percent of non-small-cell lung cancers (NSCLC), the leading cause of cancer death in the U.S. The researchers show that ROS1-driven tumors can be treated with crizotinib, which also inhibits the growth of tumors driven by an oncogene called ALK, and describe the remarkable response of one patient to crizotinib treatment.

"ROS1 encodes a protein that is important for cell growth and survival, and deregulation of ROS1 through chromosomal rearrangement drives the growth of tumors," says Alice Shaw, MD, PhD, of the MGH Cancer Center – co-lead author of the paper which has been published online in the *Journal of Clinical Oncology*. "This finding is important because we have drugs that inhibit ROS1 and could lead to the sort of dramatic clinical response we describe in this paper."

The current findings add ROS1 to the list of genes known to drive NSCLC growth when altered – a list that includes KRAS, mutations of which account for about 25 percent of cases; EGFR, accounting for 10 to 15 percent; and ALK, rearranged in about 4 percent. Altogether, known cancer-causing genetic changes have been found in a little more than half of NSCLC tumors. Originally identified in brain tumors, ROS1 rearrangement previously had been identified in one NSCLC patient and one NSCLC cell line. The current study was designed to determine the

frequency of ROS1 rearrangement in NSCLC and to define the characteristics of patients with ROS1-rearranged tumors.

The investigators screened tumor samples from more than 1,000 NSCLC patients treated at the MGH, Vanderbilt University, the University of California at Irvine, and Fudan University in Shanghai, China. ROS1 rearrangement was identified in 18 tumor samples, for a prevalence of 1.7 percent; ALK rearrangements were identified in 31 samples, with no samples showing alterations in both genes. Patients with ROS1-positive tumors tended to be younger, never to have smoked and to have a type of lung cancer called adenocarcinoma – characteristics very similar to those of ALK-positive patients.

An earlier MGH study of an experimental ALK inhibitor had found the drug suppressed the growth of a ROS1-positive cell line in addition to ALK-positive cell lines, suggesting that ROS1-positive tumors might be sensitive to the ALK-inhibitor crizotinib. This observation led corresponding author John Iafrate, MD, PhD, and his team to develop a diagnostic test that could identify ROS1-positive tumors. Around the time that test became clinically available, a lung cancer patient whose tumor had not responded to drugs targeting EGFR mutations was referred to the MGH Cancer Center for genetic testing. His tumor was negative for ALK but later proved to harbor a ROS1 rearrangement, and he was enrolled in an extension of the crizotinib clinical trial first reported in the October 28, 2010, *New England Journal of Medicine*.

"When he enrolled in the trial last April, this patient was extremely sick – with significant weight loss and very low oxygen levels – and was barely able to walk," says Shaw. "Within a few days of starting crizotinib, he felt better; and by the time we scanned his chest at seven weeks, the tumors had essentially disappeared from his lungs." Nine months after starting crizotinib therapy, this patient continues to do well. Additional ROS1-positive patients have been enrolled in this trial at

MGH, at UC Irvine and at the University of Colorado.

Provided by Massachusetts General Hospital