Native American ancestry associated with more mutations in EGFR gene among Latin Americans

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Among patients with lung cancer from Latin America, genomic and ancestry analyses revealed that Native American ancestry was associated with increased mutations in the EGFR gene, independent of smoking status, according to results from a study published in *Cancer Discovery*, a journal of the American Association for Cancer Research.

"Lung cancer is the leading cause of cancer mortality, both in the United States and globally, and understanding inherited risk factors for this disease may help us to identify populations that would benefit from increased screening efforts," said Matthew Meyerson, MD, Ph.D., director of the Center for Cancer Genomics at Dana-Farber Cancer Institute in Boston.

"Previous work has demonstrated that EGFR-mutant lung cancer is more common among populations from East Asia compared with populations from North America or Europe, about 50 percent versus 10 percent of lung cancer cases, respectively," said Meyerson, who is also a professor of genetics and medicine at Dana-Farber Cancer Institute and Harvard Medical School and an Institute Member of the Broad Institute of MIT and Harvard in Cambridge, Massachusetts. "But it is not clear whether the ethnic difference in EGFR-mutant lung cancer is due to environmental or genetic factors," he added.

Meyerson and colleagues analyzed samples from 1,153 patients with lung cancer from Latin America. Of them, 601 were from Mexico and 552 were from Colombia, and 499 patients self-reported as non-smokers. Through genomic analysis of tumor samples, the researchers identified somatic mutations in EGFR, KRAS, and other target genes.

Using a new method developed by Jian Carrot-Zhang, Ph.D., and Alexander Gusev, Ph.D., the researchers also performed ancestry analyses from tumor samples in this admixed population. Global ancestry analysis was performed to measure proportions of African, European, and Native American ancestry across the genome. Additionally, local ancestry analysis was performed, which evaluates genetic ancestry at a particular chromosomal location. Because local ancestry only evaluates a small portion of the genome, there is less potential for observed associations to be confounded by environmental exposures or socioeconomic status, which may be seen in global ancestry analyses, Meyerson explained.

Using the genomic and ancestry data, the researchers assessed the associations of somatic mutations in target genes and global ancestry groups within a single admixed population. After adjusting for a variety of factors, including self-reported smoking status and sample-specific tumor mutational burden, the researchers found that global Native American ancestry was positively correlated with mutations in the EGFR gene. Further, the researchers found that Native American ancestry was predominantly associated with oncogenic mutations in the EGFR gene, but not with non-oncogenic mutations.

Meyerson and colleagues then stratified patients by their self-reported smoking status and evaluated the association between global ancestry and mutations in target genes. In both never smokers and smokers, global Native American ancestry was associated with mutations in the EGFR gene, suggesting that the genomic differences associated with Native American ancestry are independent of smoking status.

"Smoking increases the risk for KRAS-mutant lung

cancers, while patients with lung cancer who are non-smokers more often develop EGFR-mutant lung cancer," Meyerson said. "However, we show in our study that EGFR-mutant lung cancer is also elevated among smokers with Native American ancestry."

The researchers next developed a local Native American ancestry risk score to evaluate the association of ancestry with EGFR mutation frequency across multiple distinct sites in the genome. They found that the correlation between ancestry and increased mutation frequency in the EGFR gene was stronger at the local genome level than the global genome level. "These results suggest that germline genetics–in addition to environmental factors or socioeconomic status–may have an influence on the risk of EGFR-mutant lung cancer among those with Native American ancestry," Meyerson said.

"Many lung cancers are now treatable with targeted therapy or immunotherapy," Meyerson continued. "It is very important for patients with lung cancer to undergo somatic genetic testing to determine which treatments are most likely to be effective for their particular cancer."

The study was jointly led by Meyerson; by Gusev, an assistant professor of medicine at Dana-Farber and Harvard Medical School; by Andres F. Cardona, MD, of the Clinica del Country/Foundation for Clinical and Applied Cancer Research (FICMAC) in Bogota, Colombia; and by Oscar Arrieta, MD, head of Thoracic Oncology at the Instituto Nacional de Cancerologia in Mexico City. Carrot-Zhang, a postdoctoral research fellow at Dana-Farber Cancer Institute and Broad Institute, and first author of the study, developed computational methods with Gusev and performed the bulk of the computational analyses.

Limitations of the study include a small sample size, which Meyerson noted precluded the identification of the specific gene or site in the germline that is associated with increased somatic EGFR mutations among those with Native American ancestry. Further, the researchers only tested known hotspot mutations and protein truncating mutations in lung cancer driver genes, and future work is needed to comprehensively characterize lung cancer genomes from Latin American patients, Meyerson said.

This study was supported by a Translational Research Award from the Stuart Scott Memorial Fund of the V Foundation and by the National Cancer Institute. Meyerson is an American Cancer Society Research Professor.

Meyerson is the scientific advisory board chair of OrigiMed and an inventor of patents licensed to LabCorp for the diagnosis of mutations to the EGFR gene, with pending patent applications on EGFR inhibitors. Meyerson receives research funding from Bayer, Janssen, Novo Ventures, and Ono Pharmaceutical Co.

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