LETTER TO THE EDITOR

Genetic Ancestry Affects Somatic Alterations in Lung Cancers

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The regional diversity of the genomics of non–small cell lung cancer (NSCLC) is an intriguing topic. Yet, little is known about the baseline factors—either genetic or environmental—that lead to different patterns of NSCLC-related mutations, except for tobacco-associated carcinogens. In a recent publication by Carrot-Zhang and colleagues (1), the authors presented very interesting data on patients from Colombia and Mexico and highlighted a plausible relationship between Native American genetic ancestry and somatic mutations in *EGFR*.

The authors concluded "that while controlling for global ancestry, local ancestry is associated with mutations in *EGFR* and *KRAS*, providing the first example, to our knowledge, of a germline influence" for targetable somatic events in lung cancer (1). To further the community discussion of this important topic we would like to highlight and discuss some prior evidence that also points in this direction. In a study of 444 lung adenocarcinomas from Brazilian patients (2), East Asian ancestry was independently associated with *EGFR* mutations ($P = 0.03$). In that work (2), the ancestry analysis included Asian genetic background, which differs from other efforts in Latin American populations. Because Native American ancestry shares traces of an Asian genetic background, it is possible that Asian traces could contribute to *EGFR* mutation rates. Carrot-Zhang and colleagues did not tease out Asian ethnicity in their analysis (1); hence, this remains an open question.

Another line of research looks at a unique germline variant in Brazil. *TP53* p.R337H is a germline, pathogenic variant that defines a distinct form of Li-Fraumeni syndrome (3). With regard to NSCLC, two publications in 2020 revealed an association between germline *TP53* p.R337H and development of *EGFR*-mutant NSCLC. In the first paper (4), lung adenocarcinomas were found in 5.4% (9/164) of *TP53* p.R337H carriers, and *EGFR* mutations were detected in 89% (8/9) of these patients. The prevalence of *TP53* variants at codon 337 was 5.3% (6/114) in lung adenocarcinomas harboring *EGFR* activating mutations, whereas only one case was found in the *EGFR*-wild type cohort (1/143; ref. 4). In a retrospective analysis of 513 NSCLC samples from Brazilian patients (5), *TP53* p.R337H was present in 4.3% of them and was significantly associated with somatic mutations in *EGFR* and *ERBB2* ($P < 0.00001$).

The germline factors discussed herein—Native American ancestry and the *TP53* p.R337H variant—have notoriously different backgrounds and geographic distributions. Native American ancestry tends to predominate in Central America and in countries bordering the east coast of South America, whereas the *TP53* variant is more prevalent in the south and southeast regions in Brazil (3). Despite these aspects, both features have been linked to the development of *EGFR*-mutant NSCLC. Whether Native American ethnicity and *TP53* germline mutations are truly related remains an unanswered question. In the case of *TP53* mutations, disruptive variants are expected to affect genome integrity, which facilitates other mutations to develop, but why this should specifically manifest as *EGFR* mutations is far from clear. This association should be clarified by future epidemiologic and mechanistic studies. In the work of Carrot-Zhang and colleagues (1), *EGFR* locus did not account for the association between ancestry and the occurrence of *EGFR* mutations.

Work by Carrot-Zhang and others provides relevant pieces of data to unravel the origins of somatic events that drive lung carcinogenesis. They also illustrate how admixed populations could be further studied to achieve this goal.

Authors' Disclosures

V.C. Cordeiro de Lima reports personal fees from AstraZeneca, Janssen, Merck Sharp & Dohme, Novartis, and Sanofi-Genzyme and grants and personal fees from Bristol Myers Squibb outside the submitted work. D.P. Carbone reports personal fees from AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi-Sankyo, Eisai, Eli Lilly and Company, EMD Serono, Flame Biosciences, Gene+ Technology, GlaxoSmithKline, Gritstone, and Janssen Pharmaceuticals outside the submitted work. No potential conflicts of interest were disclosed by the other author.

Published first June 2, 2021.

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Cancer Discov 2021;11:1320–1

doi: 10.1158/2159-8290.CD-20-1861

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