Letter to the Editor

Non-small cell lung cancer genomics around the globe: focus on ethnicity

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We appreciate Dr. Sekine's interest on the topic of genomic differences of non-small cell lung cancer (NSCLC) in ethnically distinct populations. In his commentary to *Journal of Thoracic Disease* (1), Dr. Sekine points the lack of comprehensive studies in this matter, and reviews the extant data. As described in his review, minority groups like African Americans (AA) are often underrepresented in relevant studies like the Lung Cancer Mutation Consortium (LCMC) (2) and The Cancer Genome Atlas (TCGA) (3), wherein most patients are self-reported as Whites. Behind this lack of specific data, several questions remain open: What is the impact of ethnicity on NSCLC development and prognosis? If there is a true association between ethnicity and NSCLC, is this related to genetic predisposition or merely related to environmental and life style factors that have been historically shared by persons in the same ethnic group?

When it comes to lung adenocarcinoma, it is intriguing to realize that a histologically similar disease may present with higher rates of *EGFR* mutations in Asian (50–60%) than in North American or European (10–20%) patients. Despite the consistency of this observation, there is no clear cause for this divergence. *EGFR* mutations tend to occur in patients with little or no smoking history, and is more often associated with low tumor mutation burden. Data from the PIONEER study—collected from 747 prospective patients in East Asia—show that even in regular smokers, this frequency can still reach 35% in that population (4). These numbers are much higher than those described in cohorts of NSCLC in Western smokers (usually lower than 5%) (5). These data suggest that smoking *per se* does not explain the clear differences observed.

If smoking is not a major factor causally related to the development of *EGFR*-mutant lung adenocarcinomas, then which factors are? Given the high rate of *EGFR*-mutant NSCLC in East Asia, genome-wide association studies (GWAS) in that population could help unravel potential risk factors. In one of the largest GWAS conducted in never-smoking Asian women, Wang *et al.* (6) have found a handful of germline single nucleotide polymorphisms (SNP) that have been related to lung cancer, some of which are present in higher minor allele frequency (MAF) in Asians. These susceptibility alleles could be related to the development of *EGFR*-mutant lung adenocarcinoma, although these data lack adequate clinical and pre-clinical (mechanistic) validation. In parallel, other factors like environmental tobacco smoke and household air pollution have been claimed as additive factors that could interact to further induce NSCLC-related *EGFR* mutations.

In this scenario of open questions, our group has put together data from NSCLC genomics in self-identified AA patients (7,8), and found that frequency of clinically relevant *driver* mutations do not seem to differ significantly from NSCLC in Western Whites. However, the overall

driver mutation rate was somewhat lower, suggesting that other, non-classical *drivers* may be present. When interpreting these data, it is important to realize that AAs have a high smoking rate, which may expectedly interfere on their lung cancer genomic landscape. Approximately 90% of patients in our AA cohort were current or former smokers, and only 24% were found to have a classic *driver* mutation in genes such as *EGFR*, *KRAS*, *ALK*, among others. One may conclude from our data that any difference in NSCLC genomics between AAs and Whites are minor, and probably not clinically relevant in the short term. In addition, larger sample sizes may be required to demonstrate such differences, particularly as related to genetic rather than self-reported ethnicity. On the other hand, understanding how these particularities relate to lung cancer development in each ethnically distinct individual may have a tremendous impact on lung cancer prevention, early diagnosis, and treatment, especially in AA patients, who share a poor prognosis overall. Determining how environmental and genetic factors shared by AAs influence lung cancer genomics in this group should be part of the next research steps.

Ethnic characterization in lung cancer studies most commonly relies on self-reported race, which is judged based on skin color or personal perceptions of identity. Self-reported race is thus often biased by a number of social and environmental factors, especially in highly admixed groups. For instance, AAs comprise an ethnic group represented by a mosaic of African and European ancestry, and each individual may phenotypically present with a different skin color tone that is subject to discrepant judgments. This matter becomes even more complicated in populations like Latin Americans, where ethnic admixture is more evident. Indeed, historical data shows that 20 times more African individuals were brought to work as slaves in Latin America and the Caribbean than in North America during the 16th to 19th centuries (9). This figure adds up to the long-term admixture that took place between Europeans and Native Americans, culminating in a phenotypically and genetically diverse population. Data from the Brazilian Institute of Geography and Statistics (IBGE) show that 43% of individuals in Brazil are self-reported as Browns (or *pardos*) (10), a concept of skin color that represents a *continuum* of race admixture. To measure the specific influence from each of these origins in an individual basis, it is recommended that genetic ancestry informative markers (AIM) be applied in studies involving admixed groups. In addition, comprehensive genomic panels may be warranted in order to define peculiarities of lung cancer genomics in these settings.

In summary, the variability of the genomic landscape of NSCLC around the globe is still a matter of much discussion. There is clear need to advance research on ethnically diverse and admixed populations such as AAs, and comprehend how lung cancer develops in each niche. Large population studies may be needed to really define genomic peculiarities, and more comprehensive panels may be necessary to define the landscape as well. In an era when precision medicine becomes a common goal in oncology, focus on the interaction of genomics with objective measures of ancestry should not be lost.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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