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Commentary

Gene by Environment Interaction Linking the Chromosome 15q25 Locus with Cigarette Consumption and Lung Cancer Susceptibility - Are African American Affected Differently? — Authors' Reply

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We appreciate Drs. Hopkins' and Young's commentary (Hopkins and Young, 2016) on some of the conclusions and limitations to our investigation (David et al., 2016) of gene by environment interactions for lung cancer in African–Americans. The investigation was not designed to examine underlying biological mechanisms of gene by environment interactions for lung cancer risk, but was instead intended to characterize the nature and directionality of such interactions in a sufficiently powered case–control study of African–Americans. Potential mediating processes, such as can be captured by measurements of airflow limitation resulting from chronic obstructive pulmonary disease and the inflammatory and oxidative stress processes – resulting from altered levels of inhaled, combusted tobacco smoke – are examples of precursor phenotypes, which could shed additional light on genetically-moderated mediation of lung cancer. The present study did not compare genetic interaction effects between different ethnic groups. Therefore, we cannot directly contrast our results with those of Asian-, American–Indian- or European-ancestry studies. Although it may appear that the dose–response of cigarettes smoked per day is lost in smokers with 2 risk alleles, this may not necessarily be the case. It may be more accurate to conclude that the genetic association with lung cancer is most prominent in light smokers. Nonetheless, our results, including the predeceasing genome-wide association studies of smoking quantity and fine mapping studies of lung cancer confirm the importance of the chromosome 15q25.1 region (CHRNA3, CHRNA5, IREB2 and PSMA4) in lung cancer risk in African–Americans. Differences in genetic architecture of this region between African-ancestry and those of non-African ancestry, such as varying prevalence of polymorphisms linked to smoking exposure and lung cancer and lower levels of linkage disequilibrium, necessitate careful evaluation within African-ancestry study populations in order to demonstrate the clinical validity of lung cancer susceptibility variants that have been more widely studied in European-ancestry populations. Overall, these results point to a complex web of causation whereby the chromosome 15q25.1 region represents a lung cancer susceptibility locus in African–Americans vis-a-vis increased smoking exposure and intrinsic lung cancer risk.

Disclosure

SPD was a scientific advisor to and is a stockholder with BaseHealth.

References

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Hopkins, R.J., Young, R.P., 2016. Gene by environment interaction linking the chromosome 15q25 locus with cigarette consumption and lung cancer susceptibility — are African–American affected differently? EBioMedicine 4, 13–14.

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