



## Commentary

# Gene by Environment Interaction Linking the Chromosome 15q25 Locus With Cigarette Consumption and Lung Cancer Susceptibility – Are African American Affected Differently?



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## ABSTRACT

The majority of lung cancer cases result from complex interactions between smoking exposure, genetic susceptibility and a person's immune response to chronic inflammation or lung remodelling. Epidemiological studies confirm that susceptibility to developing chronic obstructive pulmonary disease (COPD), especially emphysema, is also closely linked to lung cancer susceptibility. Genetic epidemiology studies have consistently reported associations between the chromosome 15q25 locus with lung cancer and COPD. In addition, studies show this locus to be independently associated with cigarette consumption and nicotine addiction in a dose-response manner, primarily at lower levels of cigarette consumption. Studies that measure both cigarette consumption and lung function, together with extensive genotype analysis, will be needed to further unravel these complex relationships.

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It is generally accepted that lung cancer results from a complex interaction between smoking exposure, chronic lung disease and genetic susceptibility (El Zein et al., 2012). Other factors found to be relevant include socioeconomic status, diet and ethnicity (Haiman et al., 2006). To what degree, and through what mechanism, does gene variation confer susceptibility to lung cancer remain to be elucidated. Furthermore, just what extent ethnicity-specific genetic and cultural effects contribute to lung cancer susceptibility also remains unclear. One feature of the genetic studies to date is the consistent association between the chromosome 15q25 locus (chr15q25), encompassing subunits of the nicotine acetylcholine receptor (*CHRNA3* and *5* genes), and cigarette consumption, lung function and lung cancer (David et al., 2016; Hung et al., 2008; Young et al., 2008).

While the results by David and colleagues appear to support prior studies, showing that the chr15q25 locus is independently associated with cigarette consumption (and by inference nicotine addiction) and lung cancer risk (David et al., 2016), there remain concerns about the exact relevance of this association. Firstly, the association with this locus encompasses as much as 4 potential candidate genes (*CHRNA3*, *CHRNA5*, *IREB2*, *PSMA4*) including several functionally relevant SNP variants found in a region where the degree of linkage disequilibrium is still to be clarified. The latter is particularly relevant in African Americans (AA) where higher recombination rates can change the

relationship between the tested variants and the functional variants underlying the phenotypic associations being reported (e.g. cigarette consumption vs lung cancer). Second, there is no consideration for the confounding or mediating effect that chronic obstructive pulmonary disease (COPD) may be having on the chr15q25 locus and its association with lung cancer (Wang et al., 2010; Young et al., 2008). This is relevant because AA have been reported to be at greater risk of COPD and greater decline in lung function, compared to Caucasians (Hopkins et al., 2015). Third, the greater risk of lung cancer reported in AA compared to Caucasians is not seen in non-smokers and is lost in heavy smokers (Haiman et al., 2006). This suggests a smoking by ethnicity interaction that is lost in heavy smokers and the possibility that susceptibility effects conferred by genetic variation may be overwhelmed. This also suggests that moderate smoking exposure creates an ethnic disparity in lung cancer risk (or incidence) not seen in never smokers or heavy smokers (Haiman et al., 2006; Hopkins et al., 2015). One of the most important features of this increased risk of lung cancer among African Americans is the apparent loss of the expected dose-response relationship between smoking exposure and lung cancer (Hopkins et al., 2015). In contrast to other ethnic groups, even light smoking exposure confers a high risk of lung cancer in AA compared to Caucasians. These observations suggest that while chr15q25 may partly determine cigarette consumption in AA (David et al., 2016), something else such as the smoker's inherent response (or susceptibility) to aero-pollutant exposure may underlie the greater disposition to lung cancer in this group. We propose that a greater susceptibility to COPD may be relevant in this setting

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(Hopkins et al., 2015). Without lung function testing, genetic epidemiology studies like that reported by David and colleagues (David et al., 2016), cannot clarify the role of unrecognized airflow limitation (COPD). The study of David and colleagues also shows that the genetic association with lung cancer in AA is only present in lighter smokers. However, ethnic differences in lung cancer incidence in the US cannot be explained by differences in smoking consumption, socioeconomic effects or diet (Haiman et al., 2006). We conclude that while AA have 1.5 fold higher lung cancer incidence than Caucasian smokers after adjustment for other risk variables (Haiman et al., 2006; Hopkins et al., 2015), it does not appear to be due to the non-genetic factors we traditionally associate with higher lung cancer risk (age, smoking exposure, diet and socioeconomic factors). That the same observation is seen for Hawaiians, argues against ethnic-specific differences in smoking practice (e.g. depth of inhalation or greater use of mentholated cigarettes) (Hopkins et al., 2015).

In a multivariable analysis, Tockman and colleagues found that airflow limitation (termed lung impairment) conferred a greater risk of lung cancer (5 fold) relative to age and pack years (1.5–2.0 fold) (Tockman et al., 1987). We suggest that there is much more to be done to elucidate the relationship between smoking exposure, lung function and immune modulation leading to pulmonary inflammatory response to smoking. In this regard it is interesting that the chr15q25 locus association with lung cancer exists in non-smokers (Ji et al., 2015). This certainly raises the possibility that factors attributable to the chr15q locus, independent of smoking consumption (and nicotine addiction), are relevant to lung cancer susceptibility which brings us back to COPD. It has been shown that *CHRNA3/5* genes are expressed on lung epithelium and mediate the lung's inflammatory response to smoking (Young et al., 2008). The ethnicity aspect is also relevant here, as the chr15q25 locus is highly conserved and may have important functions relevant to mediating lung inflammation (Young et al., 2008), where variation in immune response to pathogens is likely to result from greater evolutionary selective pressures than to variation affecting nicotine addiction (Paalani et al., 2011). Given COPD is thought to result in part from an exaggerated innate immune response, as does lung cancer, it is very hard to see how susceptibility to airflow limitation can continue to be overlooked in lung cancer studies (El Zein et al., 2012).

The take home message from the study by David and colleagues is that the chr15q25 locus, previously linked to higher cigarettes consumption and greater nicotine addiction, is similarly relevant in

smokers with African American ancestry (Young et al., 2008). However, while their findings support the hypothesis that the chr15q25 locus is independently related to cigarette consumption and lung cancer in African Americans, the exact contribution of genetic variation in this chromosomal region to lung cancer susceptibility remains far from clear.

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