POLITICAL/Confidential

GWAS in lung disease

We read with interest the recent article 'Genome-wide association studies in lung disease' by Artigas et al.1 While we agree that a greater understanding of the biological pathways underlying disease development and progression (susceptibility) will be a major outcome from these genetic epidemiological studies, we suggest other benefits may also stem from this research.

The genetics of chronic obstructive pulmonary disease (COPD) and lung cancer represent unique models for the genetics of lung disease because they result in the main from a ‘single’ measurable and preventable environmental exposure (cigarette smoking). That we can stratify for smoking exposure in these genetic association studies is critical to disease gene discovery and study design, as many of the underlying ‘susceptibility genes’ only become clinically evident (ie, expressed as disease) after several decades of daily smoking exposure. In studies of lung cancer, where cases and controls are carefully stratified by smoking exposure it appears the genes relevant to smokers are distinct to those in non-smokers.2 3 When smokers are stratified by smoking exposure and lung function, it appears that genes implicated in lung cancer overlap with those implicated in COPD.3 This might explain why COPD predates lung cancer in up to 80% of cases, conferring a two- to sixfold greater risk compared with smokers with normal lung function. By stratifying for COPD (lung function), this approach has also identified genes conferring a ‘protective’ effect in lung cancer (ie, found in healthy or resistant smokers).3 Until cigarette smoking is eradicated, understanding the biology of resistance to smoking may be of greater clinical relevance than that of susceptibility. Specifically, if the pathogenetic processes that protect smokers from COPD also protect them from lung cancer,3 then chemopreventive approaches might target these pathways. Of more immediate clinical utility is the use of genetic data (from a cheek swab) to help identify smokers at the greatest risk of COPD and/or lung cancer.3 To this end, we and others have combined genetic data with known clinical variables (eg, COPD) to develop risk models for lung cancer.3 Preliminary studies suggest such gene-based risk assessment might help motivate some smokers to quit smoking4 5 and may help target those most in need of CT screening.6 We conclude that COPD and lung cancer GWAS studies have much to contribute to respiratory medicine notably the possible basis of differential responsiveness of smokers to smoking exposure, the link between COPD and lung cancer, and the potential to develop new strategies in prevention and early diagnosis.

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