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Advances in chronic obstructive pulmonary disease genetics: building the picture one piece at a time

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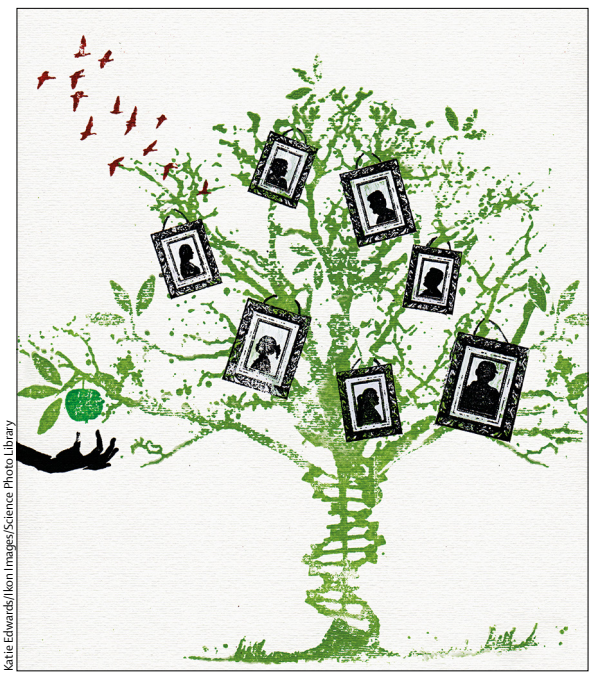
Chronic obstructive pulmonary disease (COPD) is a heterogenous disease with distinct contributions from small airways disease and emphysema, which are highly variable among individual patients. Early familial aggregation and linkage analysis studies have suggested a genetic contribution to the complex pathophysiology of COPD.[1] Impairment of pulmonary function is frequent among relatives of COPD probands, an effect that is independent of other known risk factors such as smoking, sex, race, and socioeconomic status.[2] Studies in twins have also shown substantial heritability of lung function levels.[2] With the advent of high-throughput genotyping techniques, it is now possible to complete genome wide association studies (GWASs) rapidly and fairly inexpensively. In the last few years, GWASs have identified several COPD susceptibility loci, including FAM13A, HHIP, and CHRNA3/CHRNA5/IREB;[3] however, these associations were not replicated in all studies. So, despite the impressive advances in available technology, the genetic determinants of COPD remain elusive, possibly because of its heterogeneity. As with other complex diseases, it is conceivable that such genetic determinants encompass both common variants with a modest effect size (susceptibility modifiers) and rare variants with a much stronger effect (pathogenetic variants), acting in concert to create the diverse array of COPD phenotypes.

The best known example of rare variants with a clear pathogenetic role in emphysema are mutations within *SERPINA1* gene that encodes alpha-1 antitrypsin (A1AT). A1AT is the main inhibitor of proteases in the lung and its genetic deficiency results in imbalance between the activity of proteases (mainly neutrophil elastase) and antiproteases, leading to breakdown of elastin and early-onset emphysema.[4] In *The Lancet Respiratory Medicine*, Yohan Bossé and colleagues report an inherited variant within protein tyrosine phosphatase non-receptor type 6 (*PTPN6*) gene, which leads to early-onset emphysema, suggesting that this is the second form of hereditary emphysema since the identification of A1AT deficiency in the 1960s.[5]

The authors studied a unique five-generation French-Canadian family presenting early-onset panacinar emphysema with lower lobe predominance. The family was followed in the same centre for almost 50 years and the investigators were able to recall a total of 63 family members, obtaining DNA from 55 of them. Whole-exome sequencing of 14 selected family members, followed by in-silico filtering and segregation analysis in the remaining family members, identified a very rare variant (Ala455Thr) within *PTPN6*, also known as SHP-1. The candidate variant was predicted to be deleterious by means of bioinformatic tools, a prediction that was confirmed experimentally by showing a reduced phosphatase activity of the mutant *PTPN6*.

The protein encoded by *PTPN6* is a member of the protein tyrosine phosphatase family and a key regulator of immune processes. Protein tyrosine phosphatases are known to be signalling molecules that regulate various cellular processes including cell growth, differentiation, mitotic cycle, and oncogenic transformation.[6] *PTPN6* is expressed primarily in haematopoietic cells where it functions as a negative regulator of multiple signalling activating pathways. It interacts with a wide spectrum of phosphoproteins involved in immune cell signalling and reduces their activity by dephosphorylating them. The identification of mutant *PTPN6* in this family fits well with the described immune-related mechanism in the development of emphysema.[7,8] Of importance, this observation parallels advances in emphysema caused by A1AT deficiency, with a change in paradigm from a



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pure elastase–anti-elastase imbalance to a much more complex scenario focused on adaptive immunity.[9] Bossé and colleagues highlight the important contribution of regulatory molecules involved in the normal immune homeostasis and support the concept that failure of suppression of lung immunity might well be responsible for the development of emphysema, as expected in autoimmune conditions. By analogy, dysregulation of *PTPN6* has been involved in organ-specific autoimmunity in type 1 diabetes.[10]

The segregation pattern of the Ala455Thr variant in this family is very interesting. Virtually all smoking male family members carrying the mutation had emphysema. Heterozygous female family members were apparently less prone to develop emphysema, but this is likely to be accounted for by the low prevalence of smokers in female family members. When smoking habit was taken into account, the mutation in *PTPN6* had almost complete penetrance. These results highlight the interaction between the *PTPN6* genotype and smoking exposure, suggesting that this gene might be essential in limiting immune responses to cigarette smoking, a result confirmed by the observation that current smokers have higher *PTPN6* expression than former smokers.

It should be acknowledged, however, that the *PTPN6* mutation identified by Bossé and colleagues is extremely rare, being found in only two heterozygous individuals among 135 000 genomes available outside of this study. The uncommon presentation in this family might be due to two brothers having married two sisters in the second generation, thus reducing the genetic variability of the lineage and favouring the emergence of extremely rare variants. Conversely, A1AT deficiency, although rare, is much more common (>25 cases per 100 000 in white people). As such, we should be cautious when extrapolating the findings of the present study to emphysema in general. Nevertheless, this study points to a precise mechanism whereby failure to suppress the immune response might potentially cause emphysema. It is plausible that genetic determinants of COPD are diverse and comprise both common and rare variants, each contributing to the creation of diverse COPD phenotypes. Network analyses combining different datasets are needed if we are to move beyond the analysis of single variants toward the identification of the crucial pathways responsible for emphysema. Just as in a jigsaw, each tiny piece will find its relevance only when combined in the whole picture.

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