Dissecting respiratory disease heterogeneity through the genetics of diffusing capacity

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Genome-wide association studies of physiological measurements, such as diffusing capacity, can help to explore the genetic underpinnings of respiratory disease clinical heterogeneity http://ow.ly/aXMx30ltt4f

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Genome-wide association studies (GWASs) have allowed the robust and replicable identification of novel genomic regions associated with respiratory diseases. For instance, in chronic obstructive pulmonary disease (COPD), nearly all of the described genetic risk regions were not previously known to play a role in COPD pathogenesis [1–9]. However, where sample size is critical to discovery of new genetic risk regions in GWASs, large GWASs of lung function (and lung function extremes) in the general population have made great strides in describing the genetic risk regions contributing to the observed population variability in spirometry, and in risk of COPD [10–16]. Interestingly, the genetic risk regions contributing to the observed population variability of forced expiratory volume in 1 s (FEV_1) and FEV_1 to forced vital capacity (FVC) ratio can be aggregated into genetic risk scores which are predictive of COPD [14, 16, 17].

Despite the wealth of information GWASs of COPD and lung function have provided toward understanding the genetic architecture of COPD, these studies have only marginally addressed the observed clinical and physiological heterogeneity of COPD. Machine learning techniques are one approach to discover enrichment of association of known genetic risk loci with a subgroup of COPD patients with shared clinical features [18]. The differential strength of association of COPD risk variants with COPD-related phenotypes, such as quantitative imaging features, can also be used to explore the genetic basis for COPD heterogeneity [9, 19]. Aside from these techniques, studying the genetics of sub-phenotypes and key physiological features of respiratory diseases may allow us to more directly evaluate the biological processes contributing to the clinical and physiological heterogeneity of these diseases, and in particular, COPD. GWASs of quantitative computed tomography emphysema [20, 21], despite smaller sample sizes and reduced statistical power, have demonstrated that using a more biologically specific phenotype allows discovery of variants not previously discovered in COPD GWASs, including the genome-wide significant identification of variants correlated with the first-described COPD genetic susceptibility variant, the Z allele in *SERPINA1*. Genetic studies of COPD-related clinical and physiologic features including emphysema pattern [22], emphysema distribution [23], resting oxygenation [24], pulmonary artery enlargement [25], chronic bronchitis [26] and the asthma/COPD overlap syndrome [27], have highlighted a genetic basis for the observed clinical heterogeneity of COPD and invite ongoing work into further describing the genetic susceptibility to specific features of COPD and other respiratory diseases.

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In this issue of the *European Respiratory Journal*, Terzikhan *et al.* [28] present a heritability analysis and GWAS of the diffusing capacity of the lung measured by carbon monoxide uptake (*D*LCO) as well as the transfer coefficient of the lung for carbon monoxide (*D*LCO/*V*A or *K*CO). *D*LCO and *D*LCO/*V*A are physiological traits impaired in the advanced stages of a number of complex respiratory diseases including COPD, interstitial lung disease and pulmonary hypertension. The heritability (the proportion of phenotypic variance explained by genetics) of *D*LCO was previously described in adult twins from the Swedish Twin Registry [29]; however, this is the first study examining the genome-wide genetic variant associations with either *D*LCO or *D*LCO/*V*A. In a meta-analysis of 8372 individuals from two European-ancestry studies, the Framingham Heart Study and the Rotterdam Study, the authors identified a genome-wide association of an uncommon variant (rs17280293, gnomAD European MAF 2.8%) in the *ADGRG6* (formerly known as *GPR126*) locus with *D*LCO/*V*A.

The association of rs17280293 with *D*LCO/*V*A is given additional credence since variants close to *ADGRG6* have previously been associated with FEV1/FVC ratio [10, 12–14], COPD [9] and various anthropomorphic measurements in large GWASs. Notably, recent lung function GWASs have identified two independent loci at *ADGRG6* associated with FEV1/FVC ratio [13, 14], where the lead variant at the second *ADGRG6* locus is in linkage disequilibrium (R^2=0.93 in Europeans) with rs17280293, which is associated with *D*LCO/*V*A in this journal. Terzikhan *et al.* [28] performed fine mapping and reported a 0.72 posterior probability for rs17280293 to explain the observed *D*LCO/*V*A association. Further, the authors report that rs17280293 is a missense variant predicted to be deleterious to ADGRG6 protein structure in two different functional impact prediction tools. In a separate lung tissue dataset, the authors reported significantly lower levels of *ADGRG6* in lung tissue in association with both COPD case status and lower *D*LCO/*V*A. These data suggest rs17280293 is the causal variant and *ADGRG6* is the causal gene for the *D*LCO/*V*A association at this locus. *ADGRG6* is plausible effector gene, with a role in angiogenesis. Despite this compelling evidence, a more definitive link between rs17280293 and expression or function of *ADGRG6* will need to be established.

The *ADGRG6* locus is complex. In addition to being previously described in association with lung function and COPD, variants at this locus are also associated with height, and previous studies have described two independent associations at this locus. Terzikhan *et al.* [28] assessed for possible confounding of the *ADGRG6* locus *D*LCO/*V*A association by adjusting for FEV1/FVC ratio and showed unchanged effect of rs17280293 on *D*LCO/*V*A. The association was further shown to be robust to adjustment for height as well as quantitative emphysema in a subset of individuals. These data suggest that the *ADGRG6* locus identified by the authors is independently associated with *D*LCO/*V*A level when considering FEV1/FVC ratio, height, or amount of emphysema. However, *D*LCO is a complex phenotype, affected not just by emphysema but by pulmonary vasculature and haemoglobin; *D*LCO/*V*A is further influenced by body size but does not scale monotonically with lung volume [30, 31]. The sensitivity analyses performed by the authors are subject to power considerations and further work (for example, using larger sample sizes with more detailed phenotyping and mediation analysis) will need to be done to disentangle relationship of traits at the *ADGRG6* locus marked by rs17280293 to determine if traits are truly independent in their association to the *ADGRG6* locus or if the associations are explained by un-modelled mediation of the traits by each other.

The work by Terzikhan *et al.* [28] in this issue of the *European Respiratory Journal* illustrates how the genetic study of more discrete physiologic traits, such as *D*LCO and *D*LCO/*V*A, impaired at the advanced stages of complex respiratory disease, can contribute to our understanding of the genetic basis for the clinical heterogeneity of respiratory diseases. Additionally, this study demonstrates the importance of sample size for genetic discovery and replication, where only a single loci genome-wide significant association with *D*LCO/*V*A (and not *D*LCO) was described and has yet to be replicated. Despite careful consideration of the explanatory model for the relationship of rs17280293 to *D*LCO/*V*A levels, this work highlights the difficult task left by genetic discovery, where even genetic associations with high statistical confidence mark the beginning of our journey to biologically cohesive functional descriptions of genetic loci, let alone translation to clinical relevance. In summary, Terzikhan *et al.* [28] have contributed valuable information to our understanding of complex respiratory diseases and we look forward to future larger investigation of the genetic associations and functional follow-up of *D*LCO and *D*LCO/*V*A.

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