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On Genetics, Lung Developmental Biology, and Adult Lung Function

A hypothesis is nothing but a hypothesis until proven. The fetal origins of disease hypothesis, formally the Developmental Origins of Health and Disease hypothesis, postulates that early life events may have a long-term impact on diseases and traits in adulthood (1). Such events, including environmental exposures, and developmental or pathophysiologic processes, may take place *in utero*, perinatally, or during childhood. Evidence is now accumulating that supports the Developmental Origins of Health and Disease hypothesis in that factors underpinning lung disease risk in adulthood act in early life (2–4).

In this context, Portas and colleagues (pp. 853–865) report in this issue of the *Journal* associations between lung developmental genes and adult lung function using the U.K. Biobank (5). They make use of lung development biology knowledge, selecting candidate genes to explore associations with lung function indices (Figure 1), rather than starting with an agnostic genome-wide association study (GWAS) analysis, currently a standard approach.

In the study by Portas and colleagues, almost 350,000 subjects with mean age 56 years (range, 39–70 yr) contributed cross-sectional lung function data from the well-powered U.K. Biobank (6, 7). The list of genes related to lung development was prepared by two authors, summarizing both human and experimental data in a variety of model organisms. In addition, this list was further extended to include relevant genes based on pathway information from four databases. In total, 391 genes (represented by 106,384 variants) believed to influence lung development were tested for association with prebronchodilator FVC and FEV_1/FVC. Using a two-stage and "best SNP per gene" approach, novel independent signals from 36 genes were identified and replicated internally; 16 were uniquely associated with FVC, 19 were uniquely with FEV_1/FVC, and only one signal was associated with both traits. Next, the authors used meta-analysis data from previous GWASs in the CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) and SpiroMeta consortia ($n > 100{,}000$ in both datasets) and replicated 16 variants. Pathway analyses revealed that identified genes belong primarily to the following pathways: growth factors, transcriptional regulators, cell–cell adhesion/cytoskeletal, and extracellular matrix, which was not surprising given the fact that genes were preselected based on involvement in lung development in the first place. Finally, a majority of the key SNPs were found to influence expression in the blood and/or lung tissue.

The results emerging from this methodologically sound sequence of analyses have important implications. If the missing heritability of complex traits resides at least partly in genetic variants that are missed by traditional genome-wide significance thresholds, using *a priori* knowledge to reduce the search space may be an effective approach to retrieve these missing genomic components. Using this hypothesis-driven approach, which is reminiscent of the classical candidate gene or pathway study, this study identified 16 novel variants associated with lung function that were sufficiently robust to survive both internal and external replication. Of note, although all these variants were significant after Bonferroni correction, only a few of them reached genome-wide significance in the U.K. Biobank, and none did in the external replication. Therefore, this approach identified successfully multiple novel robust genetic variants for lung function that could have been missed in a traditional GWAS. Naturally, any approach that is based on *a priori* knowledge is as good as the knowledge on which it is based. Although the authors did try to formalize their selection process of genes, it should be noted that this process eventually boils down to expert opinion and the integration of data from animal and human studies, which could be perceived as subjective. Future approaches guided by single cell–specific transcriptomic signatures obtained during different stages of lung development may represent another way to select genes and limit the search space of a GWAS (8).

Complex traits are complex not only because of their multifactorial nature but also because of their phenotypic heterogeneity. Lung function impairment is no exception, as it is associated with different profiles of risk factors and morbidities (and genetic determinants) depending on whether the "impairment" refers to FEV_1, FVC, or their ratio. Not surprisingly, in the study by Portas and colleagues, the vast majority (97%) of the identified susceptibility genes affected either FVC or FEV_1/FVC uniquely, and only one variant was associated with both indices. Although deficits in FEV_1/FVC identify the obstructive pattern and are the hallmark of chronic obstructive pulmonary disease (COPD), low levels of FVC in the presence of a conserved ratio could

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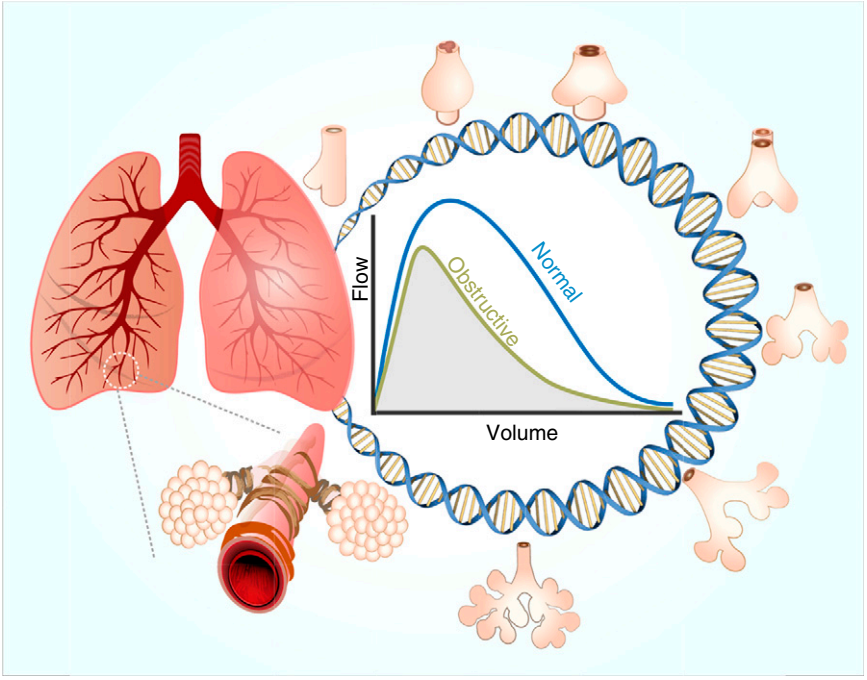

Figure 1. A schematic figure depicting the study design by Portas and colleagues. Genes known to be involved in lung development were selected as candidate genes to explore associations with lung function in adults (flow–volume indices FVC and FEV_1/FVC). Illustration by Fuad Bahram, FB Scientific Art Design.

be indicative of a spirometric restrictive pattern (albeit not diagnostic), which has been shown to carry a substantial and frequently overlooked morbidity and mortality burden in the general population (9, 10).

It is now clear that substantial heterogeneity exists also in the trajectories by which lung function patterns develop (11, 12). It has been conclusively shown that adults may develop irreversible airflow limitation, the functional hallmark of COPD, by either having an accelerated decline of FEV_1 in adult years, by reaching suboptimal maximal FEV_1 levels by young adulthood, or by any combination of the two (13). To what extent these trajectories are influenced by different molecular pathways and genetic determinants is largely unknown. By focusing on genes involved in lung development, this study captured genetic contributions that are likely relevant to a persistently low lung function trajectory into adult life. Interestingly, previous studies that tested genetic variants known to be associated with levels of adult lung function failed to find those variants to be associated with the decline of lung function (14). This suggests that the effects of genetic variants identified to date are possibly mediated more through development and growth of lung function than susceptibility to accelerated decline. The differential expression of lung function genes during fetal lung development in previous studies lends support for this observation (6, 15).

Because of the cross-sectional nature and the age range of participants in the U.K. Biobank, the study by Portas and colleagues could not address genetic contributions to lung function trajectories. We recommend that the newly identified genetic variants should be studied in the context of longitudinal lung function from cohorts that transition from childhood into adult life. This will enable the research community to fully exploit the opportunities that the fetal origins hypothesis offers to advance risk stratification and preserve lung health across the life span. ■

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Simplifying Rifapentine Dosing for Tuberculosis Treatment and Prevention

In this issue of the *Journal*, Hibma and colleagues (pp. 866–877) convey results of a population pharmacokinetic (PK) model for rifapentine based on a meta-analysis of participant-level PK data from nine clinical trials (1). These data are both relevant and timely, as evidence on the use of rifapentine for both tuberculosis (TB) treatment and prevention continues to build. Rifapentine efficacy for TB prevention was first shown in a trial of a 3-month regimen of weekly rifapentine and isoniazid (3HP; PREVENT-TB trial) and more recently in the BRIEF-TB trial, in which a 1-month daily rifapentine and isoniazid (1HP) regimen in people living with HIV was as effective as 9 months of daily isoniazid (2–4). Investigations into rifapentine use in TB treatment include an ongoing phase 3 clinical trial, the Tuberculosis Trials Consortium (TBTC) Study 31, in which rifapentine-containing regimens are being studied with the goal of shortening treatment duration to 4 months for drug-susceptible TB (5).

The excellent work by Hibma and colleagues demonstrates how models built on a robust set of pharmacology data, strengthened by inputs from multiple studies and validated by external data sets, can be utilized to inform current dosing recommendations as well guide future clinical trial design. One of the article's primary conclusions suggests that weight-based dosing of rifapentine is unnecessary, and in the authors opinion, "puts the smallest, most vulnerable individuals at risk of underexposure and, consequently, treatment failure" (1). The second major finding was that people living with HIV may require a higher dose of rifapentine compared with individuals without HIV. It is unclear as to why people with HIV have reduced rifapentine exposures, but this may lead to worsened outcomes based on rifapentine exposure–response relationships during TB treatment. However, one of the limitations of the analysis by Hibma and colleagues was the relatively low number of people with HIV included in the analysis, making up only 81 of the 863 participants. These data could be strengthened by the inclusion of PK data from BRIEF-TB, when available.

The understanding of rifapentine's pharmacology has advanced since the drug was initially U.S. Food and Drug Administration approved in 1998. Early phase one healthy volunteer studies suggested rifapentine did not induce (or increase) its own metabolism (6), which is refuted in the present work by Hibma and colleagues. By combining rifapentine PK data from nine clinical trials, the authors' population rifapentine PK model predicts the clearance of rifapentine increases 73% after repeated daily dosing, ultimately stabilizing by Day 21. Furthermore, the authors report a concentration effect on rifapentine autoinduction, which follows an maximum effect (Emax) relationship, with the greatest effect at daily doses of 300 mg, whereas the extent of autoinduction appears to plateau at doses above this amount. Conversely, intermittent dosing of rifapentine showed only minimal to moderate metabolism autoinduction.

Collectively, these new findings have implications for current treatment narratives as well as rifapentine dosing in future trials and represents a significant step forward for the field. Beginning with the implementation of the 1HP regimen, the Hibma and colleagues data

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