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Genetics, Chronic Obstructive Pulmonary Disease, and the Arrow of Time

On November 23, 1963, the day after John Kennedy died in Dallas, the city that hosted the annual meeting of the American Thoracic Society this year, a new children's television program was aired in the United Kingdom. It was called *Doctor Who* and is still running on BBC America 56 years later. Its key premise was that the Doctor could travel in space and time, thereby contravening our accepted idea that time and events flow in a linear fashion from past to future. This concept, often called time's arrow, was elegantly reviewed by the late Stephen Jay Gould in his book *Time's Arrow, Time's Cycle* (1), which contrasted the linear modern view of time with older views that could be summarized as "what goes around, comes around." From the Enlightenment onward, scientists have accepted a fairly straightforward view of cause and effect in medicine, but this approach has been challenged with the advent of "big data" and the possibility that new, nonlinear relationships will emerge that will increase our understanding of disease.

Genetics is one of the areas that have benefited most from these new computational approaches, which are essential for understanding the inherited contribution to complex multifaceted chronic conditions like chronic obstructive pulmonary disease (COPD). The recognition of the existence of specific abnormalities, such as alpha-1 antitrypsin deficiency and cutis laxa, which lead to premature emphysema, and the genetic associations of SNPs with lower lung function have stimulated the search for more genes associated with both states. Associations with some SNPs, such as the α-1 nicotinic acid receptor and hedgehog interacting protein, were relatively easy to identify (2). However, much larger studies that used genome-wide association study methodologies, including COPD-focused studies like ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoint) (3, 4) and COPDGene (5), were needed before consistent results began to emerge from groups of SNPs that predicted lower lung function or the presence of clinically diagnosed COPD. Data from the UK Biobank study added 43 new genes to the list of associations for impaired lung function in adults (6), and the search for an even better definition of these relationships continues. What is less clear is what knowledge of these genetic risk factors tells us about the functional abnormality we can measure or the structural damage that we believe should precede functional problems.

In this issue of the *Journal*, Oelsner and colleagues (pp. 721–731) provide us with new information that addresses this problem (7). They used a weighted genetic risk score (GRS) for impaired lung function based on 95 SNPs, including those already identified in multiple data sets as relating to lung function and the new candidates from the UK study (6). They determined the ability of these genes to predict either impaired lung function or a diagnosis of COPD in participants in two different populations: the MESA (Multi-Ethnic Study of Atherosclerosis) Lung cohort, a general sample of U.S. adults (8), and the SPIROMICS (Subpopulations and Intermediate Outcomes in COPD Study) cohort of smokers with or at risk of developing COPD (9). Participants in these studies had high-quality inspiratory and expiratory computed tomography (CT) scans that permitted the quantification of lung density, airway morphology, especially small airway abnormalities using parametric response mapping (10) which was available in the SPIROMICS population and the total small airway count in both population which has been reported as being in other population-based studies studying early COPD (11). Using appropriate statistical modeling and relevant sensitivity analyses, they found that the GRS predicted both the risk of impaired lung function and the chances of having moderate/severe COPD, although the explanatory power was at best modest. The GRS was associated with a range of structural abnormalities on the CT scans, especially thinner airway walls and fewer small airways. However, when they combined the CT variables with conventional clinical predictors of COPD incidence, not only did the C-statistic, a measure of the accuracy of the prediction, rise above 0.9 but the GRS contributed no additional information, irrespective of the ethnicity of the participants.

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This report has considerable strengths, especially the use of carefully characterized cohort participants and up-to-date CT analysis to define structural abnormalities in the lung. Clearly, the number of participants is modest compared with studies designed to identify new genetic predictors of disease, but the clear results here make it unlikely that a different conclusion would have been reached if more people had been recruited. More recently, investigators identified an even larger panel of genes related to lung function (12), but again it seems unlikely that inclusion of these genes in a new analysis would change the outcome.

Several important conclusions flow from this work. First, the addition of genetic profiling to the currently available approaches for predicting the occurrence of COPD is unlikely to increase detection rates. Second, evidence of small airway abnormality and reduced small airway numbers is confirmed as an early finding in damaged lungs (11). Finally, although genetic variation is related to structural change in the lung, it is the latter that predicts the functional loss and occurrence of COPD. Hence, future efforts to identify important new pathways that drive disease progression should look to structural outcomes as intermediate markers of effectiveness.

Unlike Doctor Who, we cannot travel back in time, so studies in young adults may provide a greater understanding of how genetic variation influences maximal lung function (where an individual starts) and disease progression (13). Stephen Gould believed that both time's arrow and time's cycle had value as metaphors for scientists when formulating hypotheses, but for COPD at least, the progression from structural change to functional loss over time makes time's arrow the better way to conceive of the development of this important and highly prevalent illness. ■

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