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Toward Early Detection of Idiopathic Pulmonary Fibrosis

Since their emergence as a frequent and potentially clinically meaningful finding in computed tomography (CT) screenings of smokers a decade ago (1), interstitial lung abnormalities (ILAs) have drawn significant interest and controversy. A specific set of radiologic abnormalities on chest CT scans, ILAs are relatively common and can be found in up to 10% of lung cancer screenings and older smokers (2). ILAs have traditionally been taken lightly by physicians and affected individuals alike, as symptoms in subjects with ILA are often lacking or very mild, and the prognostic significance of ILA was unknown. This has changed in recent years with the increased recognition that individuals with ILAs are at higher risk of death and exhibit higher rates of lung restriction (3–5) and that on tissue histology they often exhibit fibrosis (6). The possibility that individuals with ILAs may represent a population at risk for subsequent development of idiopathic pulmonary fibrosis (IPF) or other interstitial lung disease (ILD) is of particular importance, because of the potential for more effective interventions when the disease is diagnosed early. The connection between ILAs and pulmonary fibrosis has been supported by radiologic progression of ILAs, the presence of ILAs in asymptomatic family members of individuals with familial pulmonary fibrosis, and the significant association of ILAs with rs35705920 in the promotor region of MUC5B (Mucin 5B, oligomeric mucus/gel-forming) (4), the same gene variant that accounts for approximately 30% of cases of IPF (7). However, so far, the genetic overlap between patients with ILAs and IPF has not been studied in detail.

In this issue of the *Journal*, Hobbs and colleagues (pp. 1402–1413) performed a meta-analysis using available genome-wide data of 1,699 subjects with ILA and 10,274 control subjects from six cohorts and compared the results with genetic associations in patients with IPF (8). Because subpleural ILAs are believed to be more clinically relevant, they performed the analysis of ILAs in general and subpleural ILAs separately. In the ILA analysis, they identified three genome-wide significant associations that included the known MUC5B promoter polymorphism rs35705950 and two novel loci: rs6886640 at 5q12 near IPO11 (importin 11) and rs73199442 at 3q13 near the long noncoding RNA FCF1P3 (FCF1 pseudogene 3). In the subpleural ILA analysis—in addition to MUC5B—they identified a genetic association at the 6q15 locus with rs7744971 near HTR1E (5-hydroxytryptamine receptor 1E). None of the novel ILA loci replicated in IPF genome-wide association studies. Of the 12 reported genome-wide association study loci for IPF, only the MUC5B variant reached genome-wide significance, whereas the genetic variants near DPP9 (dipeptidyl peptidase 9), DSP (desmoplakin), FAM13A (family with sequence similarity 13 member A), and IVD (isovaleryl-CoA dehydrogenase) were nominally associated with ILA.

The findings of this study have several major implications. The most important is that although individuals with ILAs represent a population at risk for IPF, they are not synonymous with the IPF population. Only a subset of individuals with ILA exhibit a genetic risk profile that is similar to individuals with IPF, whereas others exhibit genetic associations that do not occur in IPF: the reported odds ratio is 1.97 for rs35705950 for all ILAs, and 2.22 when subsetting to subpleural ILAs, but 4.84 for IPF. None of the other IPF risk loci were significant on a genome-wide level, and all of them had a lower odds ratio in ILA. This could suggest an ILA subpopulation that is at risk of developing IPF but is being diluted by a larger fraction of subjects with ILA who do not share the same genetic risk. The finding of three novel ILA genetic associations not observed in IPF also indicates a potentially distinct entity, possibly a predisposition to other non-IPF ILDs or even the presence of gene variants that reduce the probability of progression of ILAs to fibrosis and may be protective. Regardless of their potential functional relevance, the finding of variants associated with ILA but not IPF, if replicated, could be useful developing a polygenic genetic risk profile. This is important because, currently, chest CT screenings to detect early IPF are not clinically feasible or justified. The results of this study should encourage investigators to design further studies assessing whether genetic risk profiling, potentially combined with other noninvasive biomarkers, could be used to prioritize individuals for CT screening.

Although exciting and intriguing, this study has some limitations that should be highlighted. Of course, the most obvious limitation of the discovered novel ILA associations is the lack of an independent replication cohort, but the limitations regarding the negative results should not go unnoticed. Indeed, only MUC5B reached genome-wide significance in this study, but the main study population consisted of data obtained from several cohorts that were not designed to capture early ILD. These populations differed in the definitions of ILA, the depth of phenotyping, and the original aims of the studies. Thus, it is highly possible that although the strongest association (MUC5B) was able to emerge, other valid associations simply were drowned by the sea of differences and may emerge again if comparably sized future studies are designed to detect ILAs using standard definitions, adjudicated radiological reading, and patient phenotyping.

In summary, the study by Hobbs and colleagues (8) represents a major step toward better understanding ILAs as tools for defining

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populations that should be targeted for early detection of IPF. This is a critically important mission. Although there has been considerable progress in the development of novel therapeutic options for IPF, it is highly unlikely that any of the drugs currently in the pipeline will be able to reverse the extensive lung remodeling that is often observed when patients initially present. On the other hand, it is possible that therapeutic targeting of minimal fibrotic lesions—before extensive remodeling and bronchiolization have occurred—will allow complete eradication of the disease. Thus, to truly eradicate IPF, we need a paradigm shift from focusing on developing cohorts of patients already diagnosed with IPF toward cohorts of individuals highly likely to develop the disease. We could use these cohorts to develop and test algorithms for early detection. Then we could implement a multistep strategy to eradicate IPF: identification of a population with high risk for ILA and performing chest CT screenings when appropriate; in subjects with ILA, identification of patients who will develop IPF; and last, systematic study of interventions aimed at preventing progression to IPF. In an editorial in 2012 (9) discussing an early report on ILAs (10), Dr. David Lederer compared our traditional symptom-linked diagnosis of IPF to diagnosing coronary artery disease only after the patient presented with a myocardial infarction and called for new ways for risk prediction and early detection of IPF. Seven years later, the article by Hobbs and colleagues (8) suggests that we can move forward—that we can diagnose IPF while the horse is still in the barn. ■

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The Respiratory Mucosa: Front and Center in Respiratory Syncytial Virus Disease

Infantile bronchiolitis is a major scourge of early childhood, and winter outbreaks fill the pediatric wards with wearisome regularity. Most cases are caused by respiratory syncytial virus (RSV), which was first isolated in 1956. Despite a vast amount of research in both human and animal models, a deep understanding of the inefficiency of protective immunity and, indeed, of the pathogenesis of RSV disease has been frustratingly slow to come by.

Most infants will be infected by RSV before their second birthday, with the risk of severe disease peaking at just 2 months of age. Despite the relative antigenic stability of the virus, reinfections with RSV occur throughout life. Studying disease in infants with primary disease presents considerable technical and logistical challenges; therefore, animal models (especially cotton rats, mice, and cows) have been widely used to enhance our understanding of primary infection and vaccine-enhanced disease. These models have been central in our efforts to understand the host immune response to RSV and the role of these responses in causing inflammatory bronchiolitis, but they do not recapitulate human disease in every detail.

Although animal models have advanced our understanding of the pathogenesis of bronchiolitis, a role for the type 2 immune

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