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Clinical and Genetic Associations of Objectively Identified Interstitial Changes in Smokers

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BACKGROUND: Smoking-related lung injury may manifest on CT scans as both emphysema and interstitial changes. We have developed an automated method to quantify interstitial changes and hypothesized that this measurement would be associated with lung function, quality of life, mortality, and a mucin 5B (*MUC5B*) polymorphism.

METHODS: Using CT scans from the Genetic Epidemiology of COPD Study, we objectively labeled lung parenchyma as a tissue subtype. We calculated the percentage of the lung occupied by interstitial subtypes.

RESULTS: A total of 8,345 participants had clinical and CT scanning data available. A 5% absolute increase in interstitial changes was associated with an absolute decrease in FVC % predicted of 2.47% ($P < .001$) and a 1.36-point higher St. George's Respiratory Questionnaire score ($P < .001$). Among the 6,827 participants with mortality data, a 5% increase in interstitial changes was associated with a 29% increased risk of death ($P < .001$). These associations were present in a subgroup without visually defined interstitial lung abnormalities, as well as in those with normal spirometric test results, and in those without chronic respiratory symptoms. In non-Hispanic whites, for each copy of the minor allele of the *MUC5B* promoter polymorphism, there was a 0.64% ($P < .001$) absolute increase in the percentage of lung with interstitial changes.

CONCLUSIONS: Objective interstitial changes on CT scans were associated with impaired lung function, worse quality of life, increased mortality, and more copies of a *MUC5B* promoter polymorphism, suggesting that these changes may be a marker of susceptibility to smoking-related lung injury, detectable even in those who are healthy by other measures.

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ABBREVIATIONS: COPDGene = Genetic Epidemiology of COPD; ILA = interstitial lung abnormality; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; *MUC5B* = mucin 5B; SGRQ = St. George's Respiratory Questionnaire

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Smoking-related lung disease may manifest as a variety of parenchymal diseases, including emphysema and fibrosis.[1,2] These features frequently coexist, especially in advanced disease.[3-5] Visual assessments of CT scans of smokers' lungs have revealed subtle radiologic patterns suggestive of fibrosis, some of which have been termed *interstitial lung abnormalities* (ILA).[6,7] These abnormalities are associated with mortality, as well as with a specific single nucleotide polymorphism (rs35705950) in the promoter region of the gene encoding mucin 5B (*MUC5B*), suggesting that in some cases they may indicate early or mild idiopathic pulmonary fibrosis (IPF).[8-12] However, ILA are only a subset of the broad range of the nonemphysematous patterns of lung injury evident on the CT scans of smokers, and a more comprehensive assessment of interstitial changes may be required to determine a person's susceptibility to injury from long-term tobacco smoke exposure.[13]

We have developed an automated tool that detects and quantifies interstitial and emphysematous features on the lung CT scans of smokers.[14,15] We hypothesized that interstitial features measured with this tool would be a marker of smoking-related lung injury, and, as such, would be associated with clinically significant measures such as lung function, quality of life, and mortality. In addition, given the ability of this method to detect visually identified ILA we hypothesized that these features would be associated with the presence of the *MUC5B* promoter polymorphism. Finally, we suspected that visual, spirometric, and clinical-based assessments alone may underestimate disease susceptibility. Therefore, we sought to determine whether the clinical and genetic associations with objective interstitial changes were present in those without visual ILA, in those with normal spirometric test results, and in those without chronic respiratory symptoms.

Methods

We performed our study by using CT scanning and clinical and genetic data from the Genetic Epidemiology of COPD (COPDGene) Study, which has been described in detail elsewhere.[15,16] Briefly, 10,300 smokers between the ages of 45 and 80 years, with a history of at least 10 pack-years, were enrolled and underwent baseline testing, including an extensive interview, volumetric high-resolution CT scanning of the chest, and spirometric testing. COPDGene excluded Hispanics from the study, and the only two races represented were white and black. Genotyping of the *MUC5B* promoter polymorphism (rs35705950) was performed (TaqMan Genotyping Assays; Applied Biosystems) as previously described.[8,10] Participants were excluded if their predominant lung condition was either bronchiectasis or interstitial lung disease (ILD). All participants provided written informed consent, and the overall study was approved by the institutional review boards at all of the participating centers (details available in the online supplement). This specific study was approved by the Partners Human Research Committee, protocol number 2016P001562/BWH.

The objective CT scanning analysis performed in this study has been detailed previously and is described in detail in the online supplement.[14,15] Briefly, two experts trained the tissue subtype classification tool by placing 33,865 fiducials in 138 randomly selected CT scans on radiographic features unique to each disease subtype: normal, interstitial (reticular, honeycombing, centrilobular nodule, linear scar, nodular, subpleural line, ground glass), and emphysematous (centrilobular and paraseptal). (Note that panlobular emphysema was not identified in the training cases likely because patients with α_1-antitrypsin disease were not represented in the cohort.) These training points were used to develop tissue classification vectors for each disease subtype, and de novo regions of lung were then classified based on their similarity to these vectors. Using this method, we assigned normal, emphysematous, or interstitial labels to every portion of the lung parenchyma with the results stratified by lung zone (upper, middle, and lower) (Figs 1 and 2). The aggregate of these subtype volumes summed to the total lung volume at CT scanning for each patient, and the subtype volumes were expressed as a percentage of total lung volume (ie, percentage normal, percentage emphysematous, and percentage interstitial).

The visual analysis of COPDGene CT scans for ILA has been described elsewhere.[7,12,13,15] An individual's CT scan was determined to have ILA if there were nondependent ground-glass or reticular abnormalities, diffuse centrilobular nodularity, nonemphysematous cysts, honeycombing, or traction bronchiectasis affecting more than 5% of any lung zone.[13] Individuals who had focal or unilateral ground-glass attenuation, focal or unilateral reticulation, and patchy ground-glass abnormalities (present in less than 5% of the lung) were considered to have indeterminate findings.

Statistical Analysis

We had no a priori hypothesis for the normal range of the percentage of lung occupied by interstitial features. Therefore, for all of the primary analyses, the percentage of interstitial features was evaluated as a continuous variable. Except where stated, in both the primary and subgroup analyses, effect sizes are given per a 5% absolute increase in the percentage of lung occupied by interstitial changes. This scaling was selected because it roughly approximated the SD of

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