MUC5B promoter variant: genomic fingerprint for early identification of undiagnosed pulmonary fibrosis

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The rising prevalence of pulmonary fibrosis and its attendant morbidity and mortality burden have spurred a renewed interest in the search for radiographical biomarkers predictive of early and clinically inconspicuous disease.[1] The pressing need to identify such biomarkers becomes increasingly important as these abnormalities may herald the onset of pulmonary fibrosis, which could be rapidly progressive, necessitating clinical intervention. Antifibrotic therapies have been recently demonstrated to slow the progression of pulmonary fibrosis across diverse forms of interstitial lung disease (ILD), providing some hope in those individuals shown to be at risk.[2] In this regard, high-resolution CT (HRCT) scans of the chest hold a broad appeal as a non-invasive radiological tool that is clinically accessible and rapidly performed with near-instantaneous results. Thus, a great deal of emphasis is currently placed on the recognition of radiological abnormalities that possibly signify pulmonary fibrosis in its early stages.[3] These subclinical bilateral interstitial densities, often termed interstitial lung abnormalities (ILAs) or early ILD, are frequently observed on chest HRCTs and are associated with increased risk of hospitalisation and death.[3 4] However, substantial inter-reader variability in radiologist interpretations of these fibrotic indices has led to increased reliance on deep learning algorithms and artificial intelligence to identify and accurately quantify the extent of lung parenchymal fibrosis in a more objective manner.[5]

In tandem with the rapid pace of radiological biomarker advancements is the increasing recognition of the predictive and prognostic value of genomic biomarkers associated with pulmonary fibrosis.[6] Of prime importance among the genomic biomarkers that predict risk of pulmonary fibrosis are the polymorphisms in the promoter region of the gene encoding mucin 5B (*MUC5B*) (*rs35705950*) and gene variants in the telomerase complex reverse transcriptase enzyme (*TERT*), both of which have been implicated in sporadic and familial forms of pulmonary fibrosis.[6–8] Underscoring the importance of these biomarkers is a new study by Mathai *et al* in this issue of *Thorax*, in which the authors evaluated a large cohort (n=494) of familial interstitial pneumonia (FIP) relatives from 263 FIP families across geographically disparate centres in the USA.[9] Of interest, they assessed the prevalence of these two fibrosis-associated gene variants and other risk factors for preclinical fibrosis (PrePF) in these first-degree relatives, as well as the utility of deep learning in detecting PrePF on HRCT.[9]

In this cohort, the authors performed chest HRCT scans and peripheral blood draws in those subjects aged 40 years or older who had no known diagnosis of pulmonary fibrosis. Mathai and colleagues defined a new term: 'PrePF' for individuals in this cohort deemed to have 'probable' or 'definite' fibrotic ILD on HRCT. Innovatively, they used serial deep learning techniques that leveraged a convolutional neural network algorithm with supervisory oversight from expert radiologists to objectively quantify the distinction between regions of lung tissue with and without parenchymal fibrosis. This sophisticated data-driven texture analysis was used to compute percentage pulmonary involvement, which they reported as HRCT fibrosis scores and percent high-attenuation areas. To compare variations in the minor allele frequency (MAF) of the *MUC5B* promoter variant (*rs35705950*) and the *TERT* variant (*rs2736100*) across study groups, TaqMan genotyping was performed on DNA samples obtained from peripheral blood, and regression equations were used to assess the relationship between the *MUC5B* genotype and derived quantitative indices of lung fibrosis.[9]

As might be expected, performing CT textural-based deep learning techniques in a large cohort of FIP relatives is, by itself, a vast undertaking. Using a tour de force approach, the authors coupled this highly sensitive modality to targeted genotyping to demonstrate an ontological link between the *MUC5B* risk variant and radiographical abnormalities indicative of pulmonary fibrosis. A significant minority (15.6%) had PrePF, and in these PrePF subjects, the most predominant visually identified pattern was the usual interstitial pneumonia pattern, present in over three-quarters of this subpopulation. Unsurprisingly, they identified that subjects with PrePF were older and had high minor allele frequencies of the *MUC5B* promoter variant *rs35705950* and the *TERT* variant *rs2736100*. Perhaps their most striking finding was the observation that among subjects without a prior diagnosis of pulmonary fibrosis, individuals who carried the *MUC5B* promoter variant had a greater extent of objectively quantified parenchymal fibrosis even after adjusting for known risk factors such as older age, sex and cigarette smoke inhalation when compared with non-carriers.[9]

Their findings that the quantitative extent of HRCT fibrosis was associated with visually assessed parenchymal fibrosis, breathlessness symptoms and presence of the *MUC5B* promoter variant are highly remarkable and complementary to the increasing literature linking radiographical indices of undiagnosed pulmonary fibrosis to genomic markers. Hunninghake *et al* previously demonstrated a sixfold increase in the odds of definite CT evidence of pulmonary fibrosis among individuals carrying the *MUC5B* promoter polymorphism in the general population.[7] In a separate study, Putman *et al* showed a strong association between the *MUC5B* promoter polymorphism and several fibrotic forms of ILA, including reticular abnormalities, traction bronchiectasis and honeycombing, in lungs with any zonal involvement exceeding 5%.[10] Notably, the aforementioned studies were from the general population and were not restricted to FIP relatives. In another landmark study examining a smaller cohort (n=75) of first-degree FIP relatives, Kropski *et al* characterised presymptomatic lung parenchymal abnormalities, demonstrating that visually assessed CT markers of fibrosis were prevalent in at-risk individuals and that these subjects had an increase in the MAF of the *MUC5B* promoter polymorphism.[8] However, their HRCT analyses were likely underpowered with limited ability to detect potentially significant associations.[8]

The sophisticated technique used by Mathai *et al* in quantifying the extent of HRCT fibrosis is arguably much more objective and adds a refreshing novelty to the assessment of this relationship between the *MUC5B* promoter polymorphism and lung parenchymal fibrosis.[9]

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Unsurprisingly, the association of *MUC5B* with PrePF in FIP families is modest when compared with that of the general population in which the *MUC5B* MAF is much higher, suggesting that its effect in familial disease could probably be more as a modifier gene. Furthermore, the introduction of a new terminology, PrePF, for this subpopulation is intriguing and yet might be considered debatable in light of the plethora of existing pulmonary fibrosis subcategories, which already makes disease classification with the current ILD taxonomy somewhat challenging. Thus, it might be reasonable to anticipate some hesitation before this new terminology is widely adopted for mainstream use.

These results from Mathai and colleagues open yet another portal into the realms of genomic pathophysiology in pulmonary fibrosis and could help to further elucidate our understanding of the links between the *MUC5B* polymorphism and development of fibrosis. Numerous exciting questions undoubtedly arise as we proceed along this path: can these results be uniformly extrapolated to sporadic pulmonary fibrosis? How applicable are the authors' findings to non-white populations? Does the coexistence of other genetic variants pose an additive or synergistic effect on the fibrotic risk? How strong is this dose–effect relationship between the *MUC5B* polymorphism and onset of fibrosis in other at-risk populations? Is the identified gene–fibrosis relationship of any potential pharmacogenomic or theragnostic value? The implications of the authors' investigations are immense and unquestionably increase our recognition of the role of genomic markers in defining individual risk of pulmonary fibrosis. However, much remains to be done to define the intermediary biological pathways that culminate in lung fibrosis. Epigenetic, transcriptomic and proteomic mechanisms underlying the deposition of aberrant profibrotic cells in persons at risk need additional exploration. Nevertheless, as we venture further into an era in which precision medicine continually refines our multifaceted approach to early detection and intervention, this excellent work by Mathai and colleagues holds tremendous value and will serve as a resource to guide future endeavours. While the functional importance of the *MUC5B* promoter variant is yet to be fully understood, these findings remain compelling and underscore the validity of genomic markers in phenotypic profiling of individuals with pulmonary fibrosis.

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