CHEST

CT Imaging Phenotypes of Pulmonary Fibrosis in the *MUC5B* Promoter Site Polymorphism

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BACKGROUND: To determine the effect of the *MUC5B* promoter polymorphism (rs35705950) on the CT imaging appearance of pulmonary fibrosis.

METHODS: High-resolution CT scans of 1,764 subjects were scored as part of a, genomewide association study with institutional review board approval; 1,491 of these had pulmonary fibrosis on CT scans and were included in the study. Two thoracic radiologists independently scored CT scans systematically. Discrepancies were resolved by a third thoracic radiologist. All patients were genotyped specifically for the rs35705950 single-nucleotide polymorphism (SNP). Two-tailed Fisher exact or χ^2 tests and Student *t* tests or Mann-Whitney *U* tests were used to compare proportions and means, respectively.

RESULTS: The major and minor alleles at the rs35705950 SNP are guanine (G) and thymine (T), respectively: 514 were homozygous for the major allele (G group), and 977 were heterozygous or homozygous for the minor allele (T group). The G group had a higher proportion than the T group with ground-glass opacity (62.1% vs 54.2%; $P = .04$). There was no significant difference between the G and T groups regarding presence of honeycombing. The T group showed a significantly higher subpleural axial distribution of fibrosis than did the G group (62.3% vs 42.2%; $P < .0001$). The T group showed a lower proportion of diagnoses inconsistent with usual interstitial pneumonitis (UIP; 20.3% compared with 30.5% for the G group) and a greater proportion of confident (probable UIP and UIP) UIP diagnoses (43.8% compared with 32.6% for the G group).

CONCLUSIONS: The *MUC5B* promoter polymorphism identifies a pattern of fibrosis that is different from other causes of fibrosis and may respond differently to potential therapies.

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KEY WORDS: CT imaging; idiopathic pulmonary fibrosis; *MUC5B*; rs35705950; usual interstitial pneumonitis

ABBREVIATIONS: FIP = familial interstitial fibrosis; G = guanine; IPF = idiopathic pulmonary fibrosis; SNP = single-nucleotide polymorphism; T = thymine; UIP = usual interstitial pneumonitis

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There are many secondary causes of pulmonary fibrosis. However, only a minority of patients with predispositions or exposures actually develop pulmonary fibrosis. This has led many to theorize that genetic factors as well as inherent host susceptibility predispose some people to development of pulmonary fibrotic disease. Evidence suggests that genetic mutations (eg, surfactant protein C, surfactant protein A2, and telomerase) likely play an important role in the development of pulmonary fibrosis in a substantial minority of cases.[1-4] Seibold et al[5] showed that the rs35705950 single-nucleotide polymorphism (SNP), a probable promoter site of an airway mucin gene (*MUC5B*), is associated with idiopathic pulmonary fibrosis (IPF) and familial pulmonary fibrosis. This finding has been validated in multiple separate study cohorts.[6-13] Other studies failed to show an association between the *MUC5B* promoter polymorphism and other causes of pulmonary fibrosis, suggesting that it may be specific to IPF.[6,8,14]

IPF is the most common subtype of the idiopathic interstitial pneumonias. Despite its relative frequency, the underlying cause of IPF is unknown. The typical findings of IPF on chest CT scans are that of usual interstitial pneumonitis (UIP): reticular abnormality with peripheral and basilar preponderance, presence of subpleural honeycombing, and absence of other features suggestive of an alternative diagnosis. There is little information about the CT imaging pattern of pulmonary disease in subjects with genetic causes of pulmonary fibrosis. A large study of 340 subjects evaluating the CT imaging pattern in familial interstitial fibrosis (FIP) showed that the imaging pattern in FIP was dissimilar from that of sporadic IPF/UIP.[15] However, this study did not evaluate imaging findings relative to specific genetic mutations and likely included multiple heterogeneous genetic variations with similar phenotypes. To our knowledge, there is no study that has extensively evaluated the CT imaging appearance of pulmonary fibrosis relative to a specific genetic variation. The purpose of this study was to detail the CT imaging phenotype of pulmonary fibrosis regarding the *MUC5B* promoter site (rs35705950) polymorphism, which has been strongly associated with both IPF and familial pulmonary fibrosis.[5-10] The major allele at this SNP is guanine (G), and the minor allele is thymine (T). On the basis of previous studies that have shown that the T allele is associated with dominant expression of IPF, we hypothesized that the CT imaging patterns of those with the T allele (whether heterozygous or homozygous) at the rs35705950 SNP would be more consistent with a UIP pattern than would that of those with the G allele.

Materials and Methods

This case control study was approved by our institutional review board (NJH 1441A). Informed consent was obtained from all subjects.

Study Population

A cohort of subjects (self-reported white) with pulmonary fibrosis was recruited from multiple sources including National Jewish Health, the Lung Tissue Research Consortium, Vanderbilt University, University of California San Francisco, the InterMune-supported IPF γ-interferon l and pirfenidone trials, and a cohort of known families with FIP from 1999 to 2010. A total of 1,914 subjects were genotyped from this group. CT scans of the chest were available for review in 1,764 subjects. In a prior study, we reported on 201 of the 1,764 subjects included in the current study.[16] The prior report only included subjects with pathologic correlation; the current study expands on this by having a much larger subject number and includes new evaluation of the CT imaging pattern of pulmonary fibrosis relative to the *MUC5B* promoter site polymorphism. Of the 1,764 subjects, 1,491 had evidence of pulmonary fibrosis on chest CT scans and were included in our study.

CT Imaging Evaluation

Two thoracic radiologists (J. C. and A. C.; approximately 6-8 years of experience in chest imaging) scored the chest CT scans independently. Discrepancies were resolved by a third chest radiologist (D. L.; 23 years of experience in chest imaging). All readers were blinded to histopathologic, clinical, and genotypic data. CT scans were scored for pulmonary fibrosis, honeycombing, and ground-glass opacity as defined by the Fleischner glossary of terms. Pulmonary fibrosis was considered present if there was reticular abnormality and/or subpleural irregularity or traction bronchiectasis with or without honeycombing. Preponderance of disease distribution was scored in both the zonal (upper, middle, lower, diffuse) and axial (peribronchovascular, peripheral, diffuse) planes when possible. Presence or absence of pulmonary fibrosis, honeycombing, and ground-glass opacity was scored on a three-point scale (none, probable, or definite). Percentage lung involvement regarding pulmonary fibrosis, honeycombing, and ground-glass opacity was scored to the nearest 10%.

Readers were allowed to select any diagnosis or combination of diagnoses including the whole spectrum of the idiopathic interstitial pneumonias, hypersensitivity pneumonitis, asbestosis, silicosis, sarcoidosis, obliterative bronchiolitis, and cellular bronchiolitis with level of confidence. If a single diagnosis was scored as definite, then no other diagnoses were scored. Confidence of diagnosis specific to UIP was scored as inconsistent with UIP, indeterminate UIP, probable UIP, or UIP depending on the radiologists' opinion of the likelihood of the diagnosis based on imaging findings (Figs 1-4).[16-19] A UIP pattern was defined as basilar and peripheral preponderant fibrosis with honeycombing and absence of features to suggest another alternative diagnosis. Probable UIP was defined as basilar and peripheral preponderant fibrosis with little or no honeycombing and absence of features to suggest another alternative diagnosis. Inconsistent with UIP was defined according to current guidelines in IPF diagnosis.[20] Indeterminate UIP was defined as pulmonary fibrosis with imaging features not sufficiently specific to reach a level of diagnosis that was