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

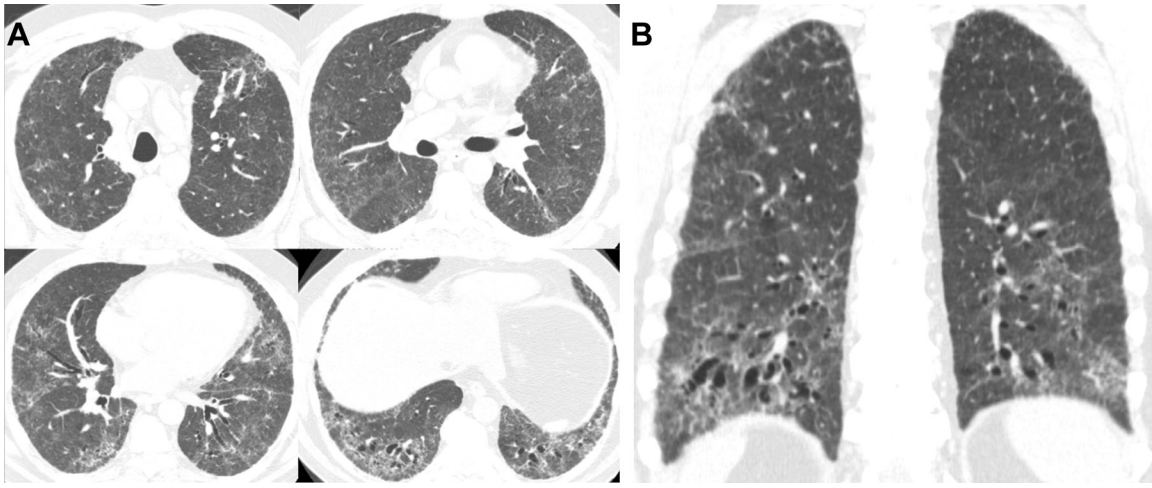

Figure 1 – *A-B, Multiple axial (A) and coronal (B) images from chest CT imaging in a 62-year-old man with GG genotype at the rs35705950 single-nucleotide polymorphism show basilar and peribronchovascular predominant pulmonary fibrosis characterized by ground-glass opacity, reticulation, and traction bronchiectasis without subpleural honeycombing. The CT scans were scored as inconsistent with usual interstitial pneumonitis because of the peribronchovascular predominance.*

definite, probable, or inconsistent with UIP; these were cases in which the CT imaging pattern was intermediate between that of probable UIP and inconsistent with UIP (eg, mild to moderate degree of air trapping, mild ground-glass opacity slightly more prominent than reticulation) or the axial or zonal distribution was diffuse (which is not addressed in current guidelines). The vast majority of indeterminate UIP and probable UIP CT imaging cases in this study would be categorized as possible UIP on CT scans according to current guidelines.[20]

Genotyping Assay

All subjects were genotyped for the *MUC5B* promoter polymorphism (rs35705950). *MUC5B* SNP genotypes were determined using TaqMan genotyping (Life Technologies) as reported in a previous publication.[5]

Statistical Analysis

We used χ^2 tests to test for any association between groups. A two-tailed Fisher exact test was used when cell counts were expected to be less than 5, and Monte Carlo estimates were used for statistical analysis for tables exceeding a 2×2 configuration. Two-tailed Student *t* tests and Mann-Whitney *U* tests were used to compare means. A *P* value $< .05$ was considered statistically significant for all tests. All statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc).

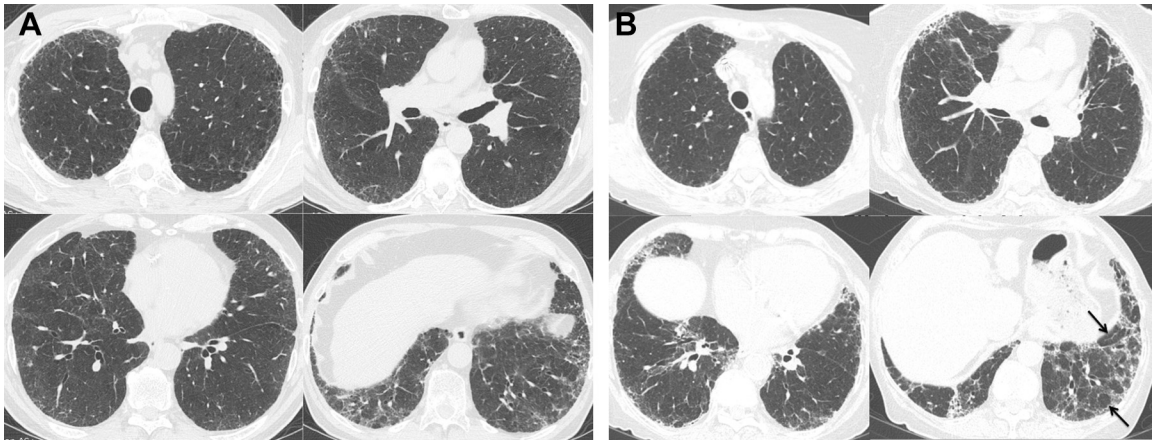

Figure 2 – *A, Multiple axial images from chest CT imaging in a 57-year-old man with GT genotype at the rs35705950 single-nucleotide polymorphism (SNP) show mild basilar and peripheral predominant pulmonary fibrosis characterized by ground-glass opacity, reticulation, and traction bronchiectasis without subpleural honeycombing. These CT scans were scored as indeterminate usual interstitial pneumonitis (UIP) given the low level of confidence in making a UIP diagnosis. B, Multiple axial images from chest CT imaging in a 62-year-old woman with GG genotype at the rs35705950 SNP show mild peripheral and basilar predominant reticulation and traction bronchiectasis without subpleural honeycombing. There is moderate degree of mosaic attenuation (arrows) in the basilar left lower lobe and mild mosaic attenuation in the right lower lobe, shown to represent air trapping on expiratory images (not shown). These CT scans were scored as indeterminate UIP given the borderline degree of air trapping.*

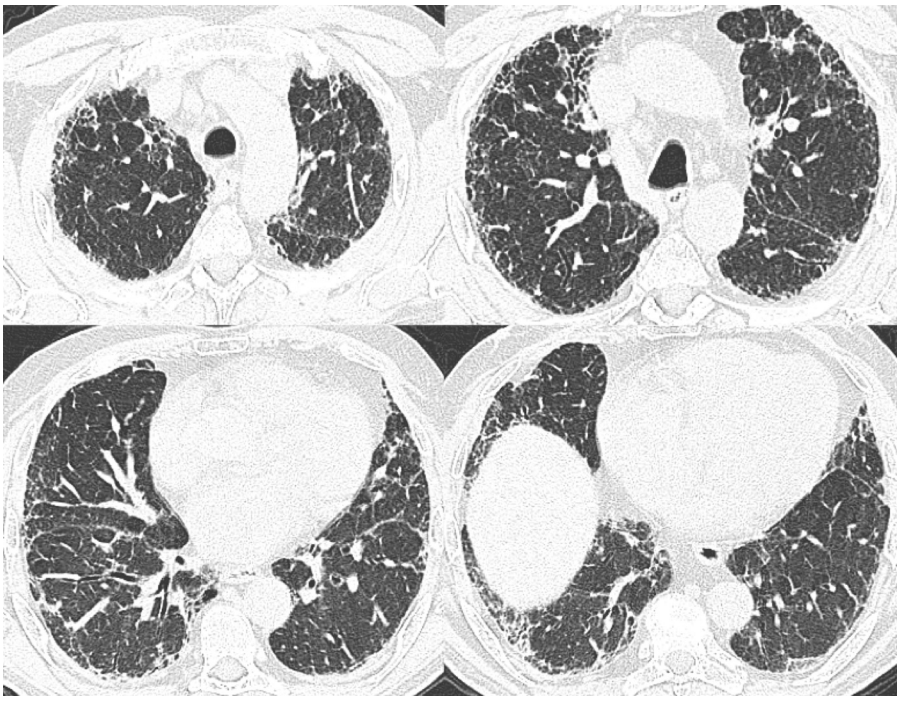

Figure 3 – *Multiple axial images from chest CT imaging in a 55-year-old man with GT genotype at the rs35705950 single-nucleotide polymorphism show mild peripheral predominant pulmonary fibrosis characterized by reticulation and traction bronchiectasis without subpleural honeycombing. These CT scans were scored as probable usual interstitial pneumonitis given the absence of definite subpleural honeycombing.*

Results

The major and minor alleles at the rs35705950 SNP are G and T, respectively. There were 514 GG (G group) and 977 GT or TT (T group) subjects. The heterozygous GT group and the homozygous TT group were combined based on the dominant allele model.[21]

Demographic Characteristics

The study subject demographic characteristics are detailed in Table 1. Demographic characteristics between the G and T groups were similar except that the T group was older than the G group, though this difference was quantitatively small. The average ± SD age, percentage female, and percentage with smoking history in the G group were 63.3 ± 10.3 years, 34%, and 66%, respectively. The average age, percentage female, and percentage with smoking history in the T group were 67.0 ± 8.0 years, 32%, and 67%, respectively.

Summary of Radiographic Findings

In those in whom honeycombing could be confidently scored by two or more readers, 48.8% (682 of 1,398) had

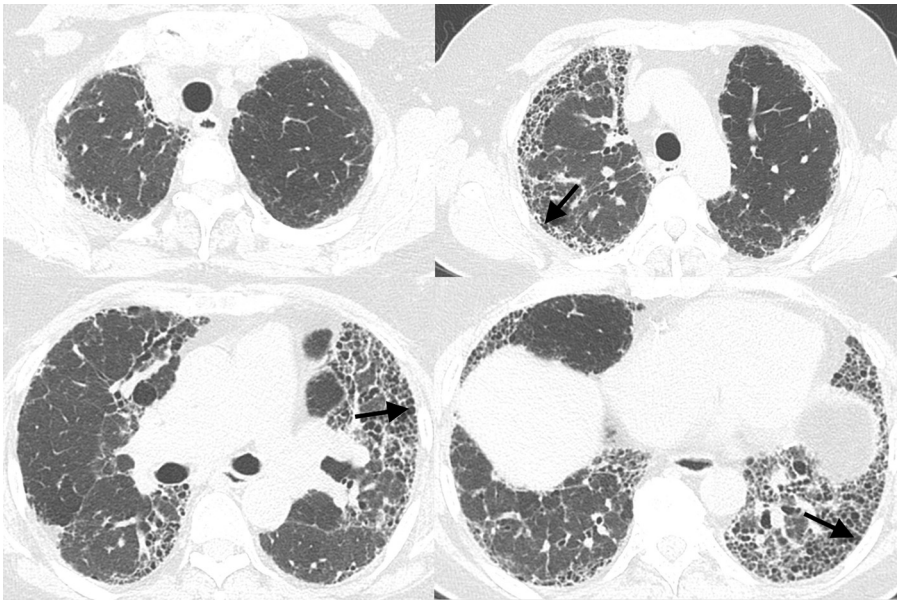

Figure 4 – *Multiple axial and coronal images from chest CT imaging in a 72-year-old man with GT genotype at the rs35705950 single-nucleotide polymorphism show basilar and peripheral predominant pulmonary fibrosis characterized by reticulation and traction bronchiectasis with subpleural honeycombing (arrows) without other findings to suggest an alternative diagnosis to usual interstitial pneumonitis (UIP). The CT scans were scored as UIP.*

TABLE 1] Basic Demographic Characteristics of Subjects Relative to the rs35705950 Single Nucleotide Polymorphism

Subject[a] Characteristic by *MUC5B* Genotype	GG (n = 514)	GT/TT (n = 977)
Sex (female), No. (%)	176 (34)	313 (32)
Age at CT scan, y, mean ± SD[b]	63.3 ± 10.3	67.0 ± 8.0
Smoking History (Ever), No. (%)	302 (58.8)	595 (60.9)
Ethnicity, No. (%)		
Hispanic	7 (1)	10 (1)
Non-Hispanic	386 (75)	709 (73)
Unknown	121 (24)	258 (26)

G = guanine; T = thymine.
[a]Self-identified as white with radiologic evidence of fibrosis and available genotypes.
[b]Student *t* test $P < .001$.

honeycombing. In those in whom ground-glass opacity could be confidently scored by two or more readers, 56.9% (575 of 1,011) had ground-glass opacity. The average percentage of involved lung among all subjects for total lung fibrosis, honeycombing, and ground-glass opacity were 22.5% ± 10.1%, 5.3% ± 6.2%, and 19.1% ± 10.4%, respectively. The majority of subjects in whom a confident zonal (61.0% [910 of 1,491]) and axial (76.1% [1,135 of 1,491]) distribution of fibrosis could be determined demonstrated pulmonary fibrosis predominant in the lower (57.9%) and peripheral (55.2%) lung. In terms of UIP diagnosis, 23.8% (328 of 1,377) were scored as not UIP, 36.2% (499 of 1,377) as indeterminate UIP, 19.6% (270 of 1,377) as probable UIP, and 20.3% (280 of 1,377) as UIP. Using current guidelines in which the probable and indeterminate UIP CT imaging patterns are combined into a single possible UIP CT imaging pattern, the proportion of UIP CT imaging diagnoses would be as follows: 23.8% (328 of 1,377) not UIP, 55.8% (769 of 1,377) possible UIP, and 20.3% (280 of 1,377) UIP. In 114 of the 1,491 subjects, the CT scans were considered inadequate for UIP diagnostic assessment.

TABLE 2] Presence of Honeycombing Relative to the rs35705950 Single Nucleotide Polymorphism

MUC5B Genotype	Honeycombing, No. (%)		
	No	Probable	Definite
GG	247 (51)	55 (11)	182 (38)
GT/TT	469 (51)	110 (12)	335 (37)

χ^2 $P = .90$. See Table 1 legend for expansion of abbreviations.

Findings of Pulmonary Fibrosis in Relation to rs35705950

The percentage of subjects with honeycombing (Table 2) was not significantly different between the G and T groups (49.0% [237 of 484] vs 48.7% [445 of 914], respectively). There was a higher percentage of subjects in the G group than in the T group who had ground-glass opacity (62.1% [213 of 343] vs 54.2% [362 of 668], respectively; $P = .04$) (Table 3). The G and T groups did not differ significantly in average percentage of lung involvement for total lung fibrosis, honeycombing, and ground-glass opacity (Mann-Whitney *U* test *P* values of .24, .98, and .49, respectively).

Predominant Zonal and Axial Distribution of Pulmonary Fibrosis in Relation to rs35705950

The proportions of predominant zonal and axial distribution of pulmonary fibrosis are summarized in Table 4. There was no statistical difference in the zonal distribution of pulmonary fibrosis relative to the *MUC5B* promoter site polymorphism. However, the G group showed a lower proportion of subpleural (G, 42.2% [168 of 398] vs T, 62.3% [459 of 737]) and a higher proportion of peribronchovascular (G, 26.1% [104 of 398] vs T, 12.5% [92 of 737]) pulmonary fibrosis than did the T group ($P < .0001$).

UIP Diagnosis Relative to rs35705950

The proportion of CT imaging UIP diagnoses relative to the rs35705950 SNP is summarized in Table 5 according to the CT imaging scoring system in the current study methodology and that in current guidelines. There was a statistically significant difference between the proportion of CT imaging UIP diagnoses ($P < .0001$). The G group showed a higher proportion of diagnoses inconsistent with UIP (30.5% compared with 20.3% for the T group) and a lower proportion of confident (probable UIP and UIP) UIP diagnoses (32.6% compared with 43.8% for the T group).

TABLE 3] Presence of Ground-glass Opacity Relative to the rs35705950 Single Nucleotide Polymorphism

MUC5B Genotype	Ground-glass Opacity, No. (%)		
	No	Probable	Definite
GG	130 (38)	39 (11)	174 (51)
GT/TT	306 (46)	73 (11)	289 (43)

χ^2 $P = .04$. See Table 1 legend for expansion of abbreviations.

TABLE 4] Zonal and Axial Distribution of Pulmonary Fibrosis Relative to the rs35705950 Single Nucleotide Polymorphism

MUC5B Genotype	Zonal Distribution (Consensus), No. (%)[a]				Axial Distribution (Consensus), No. (%)[b]		
	Diffuse	Lower	Middle	Upper	Diffuse	Peribronchovascular	Subpleural
GG	119 (36)	184 (56)	8 (2)	18 (5)	126 (32)	104 (26)	168 (42)
GT/TT	200 (34)	343 (59)	15 (3)	23 (4)	186 (25)	92 (12)	459 (62)

Only high confidence distribution data was included in the study. See Table 1 legend for expansion of abbreviations.
[a]Not statistically different.
[b]χ^2 $P < .0001$.

Discussion

There is growing interest in the relationship of the rs35705950 SNP variant and pulmonary fibrosis; however, to our knowledge, no studies have systematically reported the chest CT imaging manifestations relative to this SNP.[5,7,8,10,14,22] Multiple separate studies have shown a strong association between IPF and the T minor allele.[6-13] The odds ratios for pulmonary fibrosis among subjects who were heterozygous and those who were homozygous for the T minor allele of this SNP were 9.0 (95% CI, 6.2-13.1) and 21.8 (95% CI, 5.1-93.5) in the original description.[5] Our results showed significant differences in the pattern of pulmonary fibrosis on CT scans relative to the rs35705950 SNP, with the T group showing a lower proportion of ground-glass opacity, higher proportion of subpleural distribution, and higher proportion of confident UIP diagnoses.

In UIP, there is peripheral and basilar predominant pulmonary fibrosis on CT scans in approximately 90% to 100% and 70% to 75% of cases, respectively.[17,19,23-26] In our study, the T group more often demonstrated the typical axial distribution of UIP than did the major allele group; this likely led to a higher percentage of UIP and probable UIP scores in these subjects than in those in the G group. We theorize that subjects who carry the minor T allele at the rs35705950 SNP, and then develop pulmonary fibrosis, are more likely to develop the typical imaging manifestations of UIP/IPF. This is supported by the strong association between IPF and the *MUC5B* polymorphism in previous studies.[6-13] If this is true, this SNP would be an important marker in those at risk for pulmonary fibrosis.

The complex relationship between CT imaging appearance with genetics and survival has not yet been adequately studied. Although the UIP pattern of pulmonary fibrosis usually portends poor prognosis, other nonimaging findings can augment survival in patients with pulmonary fibrosis. Previous studies have explored the advantage of combining nonimaging data with chest CT scans to predict patient prognosis in the setting of pulmonary fibrosis.[17,27] Flaherty et al[17] showed that subjects with histologic UIP without a confident high-resolution CT imaging diagnosis of UIP had better survival than did subjects with histologic UIP and a confident high-resolution CT imaging diagnosis of UIP. Park et al[27] found that subjects with collagen vascular disease-related UIP had superior survival relative to those with idiopathic UIP, showing that the setting in which pulmonary fibrosis occurs is still pertinent regardless of imaging findings.

TABLE 5] Proportion of UIP Diagnoses on Chest CT Scans Relative to the rs35705950 Single Nucleotide Polymorphism

CT Imaging Scoring System and *MUC5B* Genotype	UIP, No. (%)			
	Inconsistent With UIP	Indeterminate for UIP	Probable UIP	UIP
Current study				
GG	145 (31)	175 (37)	79 (17)	76 (16)
GT/TT	183 (20)	324 (36)	191 (21)	204 (23)
			Possible UIP	
Current guidelines				
GG	145 (31)	…	254 (54)	76 (16)
GT/TT	183 (20)	…	515 (57)	204 (23)

In a small subset of subjects, concordant diagnosis could not be established and were excluded from this portion of the analysis. χ^2 $P < .0001$. UIP = usual interstitial pneumonitis. See Table 1 legend for expansion of other abbreviations.

The rs35705950 SNP may be another promising biomarker in predicting patient prognosis and possibly optimal treatment. A 2013 study showed that the minor allele variant at the *MUC5B* promoter site polymorphism is associated with increased rather than decreased survival among those with IPF.[7] The adjusted hazard ratio for those who were homozygous for the minor allele (TT) was 0.15 to 0.23 relative to those who were homozygous for the major allele (GG), and the adjusted hazard ratio for those who were heterozygous was 0.39 to 0.48. In the general population, the minor allele appears to predispose individuals to development of pulmonary fibrosis and has been most strongly associated with IPF—the most fatal form of pulmonary fibrosis.[8,14,22] The mechanism behind this seemingly contradictory juxtaposition of associations has not yet been studied but may be related to improved innate immune host defense.[28,29] In our study, the T group had a lower prevalence of ground-glass opacity. Ground-glass opacity is a relatively nonspecific CT imaging finding; however, in the setting of pulmonary fibrosis, superimposed diffuse alveolar damage representing acute exacerbation of pulmonary fibrosis (associated with poor prognosis) is a consideration.[30,31] A study evaluating the synergy of combining *MUC5B* promoter polymorphism and CT imaging data in survival prognostication would be the obvious next logical study to pursue.[17,32-34]

The G group had a CT imaging pattern more often inconsistent with UIP and a higher rate of peribronchovascular distribution (suggestive of nonspecific interstitial pneumonia) than did the T group.[20] It is likely that a greater proportion of the G group had a secondary form of pulmonary fibrosis rather than IPF. Stock et al[8] showed a lack of an association between pulmonary fibrosis in subjects with scleroderma (usually nonspecific interstitial pneumonia) and sarcoidosis with the rs35705950 SNP, implying that this variant likely does not constitute a shared fibrotic mechanism across all fibrotic lung diseases. Instead, the authors suggested that the rs35705950 SNP variant is associated with an IPF-specific pathway, differing from fibrotic lung disease related to underlying immunologic/inflammatory causes. Peljto et al[14] also found no association between interstitial lung disease in subjects with scleroderma and the rs35705950 SNP.

Our study had some limitations. We did not attempt to compare imaging scoring with the true gold standard in diagnosis of interstitial lung disease—multidisciplinary radiology/pathology/clinical correlation. However, the accuracy of high-resolution CT imaging in UIP diagnosis is 80% to 90% when a trained radiologist chooses UIP as the first choice diagnosis.[19,24,25] When a confident diagnosis of UIP is made at high-resolution CT imaging (peripheral and basilar predominant pulmonary fibrosis with subpleural honeycombing and no other features to suggest an alternative diagnosis), the accuracy increases to 90% to 100%. Therefore, the divergence between the percentage of confident UIP diagnoses based on CT scans between the G and T groups should not be discounted. Furthermore, the purpose of this study was not to assess the true diagnostic proportion of patients with the *MUC5B* promoter site polymorphism but rather to show that patients with different genotypes relative to this SNP have different imaging phenotypes. We also did not assess any underlying genetic mutations other than the specified *MUC5B* promoter site polymorphism, which may have augmented the CT imaging phenotype. However, the *MUC5B* promoter polymorphism is the strongest genetic risk factor for pulmonary fibrosis and currently the only one that has been consistently replicated.

In conclusion, variation at the rs35705950 SNP is associated with different phenotypes of pulmonary fibrosis on chest CT scans. The T group was more likely to demonstrate a subpleural predominant pattern of pulmonary fibrosis and a UIP pattern on chest CT scans. The G group more often demonstrated a CT imaging pattern inconsistent with UIP. This difference in CT imaging appearance across this SNP suggests that integration of imaging findings and genetic data may be valuable biomarkers in patients with interstitial lung disease and highlights the need for more research in the genetics of interstitial lung disease. The minor allele at this SNP has already been shown to be a valuable biomarker in predicting superior patient survival. The next step would be a study evaluating the synergy of this SNP combined with CT imaging findings in predicting patient outcome. Future work in a larger cohort with imaging, histologic examination, genetic data, and outcome measures (such as survival and response to treatment) should be pursued.

Acknowledgments

Author contributions: J. H. C. takes responsibility for (is the guarantor of) the content of the manuscript, including the data and analysis. J. H. C., A. L. P., and D. A. L. designed the study. J. L. T. coordinated the clinical evaluations. J. H. C., A. C., and D. A. L. performed radiological phenotyping of study subjects. D. F. M. managed the database. A. L. P. and T. E. F. analyzed data. A. L. P. created tables. J. H. C., A. L. P., M. I. S., D. A. S., and D. A. L. provided advice on design and interpretation of results. J. H. C., A. L. P., D. A. S., and D. A. L. performed literature review. J. H. C., A. L. P., M. I. S., D. A. S., and D. A. L. wrote and edited the manuscript.

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