CT Scan Findings of Probable Usual Interstitial Pneumonitis Have a High Predictive Value for Histologic Usual Interstitial Pneumonitis

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BACKGROUND: The current usual interstitial pneumonitis (UIP)/idiopathic pulmonary fibrosis CT scan classification system excludes probable UIP as a diagnostic category. We sought to determine the predictive effect of probable UIP on CT scan on histology and the effect of the promoter polymorphism in *MUC5B* (rs35705950) on histologic and CT scan UIP diagnosis.

METHODS: The cohort included 201 subjects with pulmonary fibrosis who had lung tissue samples obtained within 1 year of chest CT scan. UIP diagnosis on CT scan was categorized as inconsistent with, indeterminate, probable, or definite UIP by two to three pulmonary radiologists. Tissue slides were scored by two expert pulmonary pathologists. All subjects with available DNA (N = 200) were genotyped for rs35705950.

RESULTS: The proportion of CT scan diagnoses were as follows: inconsistent with (69 of 201, 34.3%), indeterminate (72 of 201, 35.8%), probable (34 of 201, 16.9%), and definite (26 of 201, 12.9%) UIP. Subjects with probable UIP on CT scan were more likely to have histologic probable/definite UIP than subjects with indeterminate UIP on CT scan (82.4% [28 of 34] vs 54.2% [39 of 72]; $P = .01$). CT scan and microscopic honeycombing were not associated with each other ($P = .76$). The minor (T) allele of the *MUC5B* polymorphism was associated with concordant CT scan and histologic UIP diagnosis ($P = .03$).

CONCLUSIONS: Probable UIP on CT scan is associated with a higher rate of histologic UIP than indeterminate UIP on CT scan suggesting that they are distinct groups and should not be combined into a single CT scan category as currently recommended by guidelines. CT scan and microscopic honeycombing may be dissimilar entities. The T allele at rs35705950 predicts a UIP diagnosis by both chest CT scan and histology. CHEST 2015; 147(2):450-459

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ABBREVIATIONS: IPF = idiopathic pulmonary fibrosis; SNP = single nucleotide polymorphism; UIP = usual interstitial pneumonitis

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Idiopathic pulmonary fibrosis (IPF) is the most common form of pulmonary fibrosis, and usual interstitial pneumonitis (UIP) is its histologic and imaging correlate. Studies have shown that genetic risk factors are associated with the development of pulmonary fibrosis.¹ Pulmonary fibrosis occurs with mutations in the surfactant protein C gene, surfactant protein A2 gene, and telomerase genes.²⁻⁴ Seibold et al⁵ showed that the minor allele (Thymidine [T]) of the single nucleotide polymorphism (SNP) rs35705950, within the promoter region of an airway mucin gene (*MUC5B*), is associated with both familial and sporadic forms of IPF,⁵ and this has been validated in five independent study populations.⁶⁻¹⁰ However, this variant was not associated with sarcoidosis or the pulmonary fibrosis that occurs in scleroderma.^{6,11,12}

Prior studies examined the correlation between CT scan and histologic findings in the setting of pulmonary fibrosis.¹³⁻¹⁸ These suggest that though a highly confident diagnosis of UIP on CT scan is strongly predictive of IPF, the overall sensitivity of CT scan for a UIP diagnosis is approximately 50%.¹⁹⁻²² For this reason, current guidelines suggest that subjects without a confident CT scan diagnosis of UIP, those with a CT scan appearance of possible UIP or inconsistent with UIP, should be considered for surgical lung biopsy.²³ There is likely a subpopu-

lation of subjects without CT scan honeycombing but with otherwise typical features of UIP (termed probable UIP in this study) that are highly likely to have UIP.²⁴ The probable UIP CT scan group (as defined in this study) would be considered a subset of possible UIP on CT scan using current guidelines.²³ The significance of probable UIP CT scan in establishing a UIP diagnosis is unknown. Moreover, there are no studies which have evaluated the relationship between histologic and radiologic diagnoses of UIP relative to the rs35705950 SNP genotype.

The purpose of this study was to determine the positive predictive value of probable UIP on CT scan for histologic UIP. A secondary goal of the study was to determine whether the *MUC5B* promoter site SNP (rs35705950) is associated with concordant radiologic and histologic diagnosis of UIP.

We hypothesized that the CT scan finding of probable UIP would have a high predictive value for histologic UIP. Given the association between the minor allele (T) at the *MUC5B* promoter site polymorphism and IPF, we also hypothesized that the imaging and histologic diagnosis in those with the minor allele (T) would be more often UIP compared with those with the major allele (Guanine [G]).

Materials and Methods

This Health Insurance Portability and Accountability Act (HIPAA) compliant study was approved by our institutional review board (NJH 1441A). This study was conducted in accordance with the amended Declaration of Helsinki. Consent was obtained from all subjects.

Study Population

Clinical, imaging, histologic, and genetic data were collected from subjects with known or suspected pulmonary fibrosis. Subjects were not limited to those with UIP on histology and imaging or a clinical diagnosis of IPF. These subjects were taken from multiple studies and centers: National Jewish Health; the National Heart, Lung, and Blood Institute (NHLBI) Lung Tissue Research Consortium; Vanderbilt University; University of California San Francisco; the InterMune-supported IPF γ -interferon I and pirfenidone trials; and families with familial interstitial pneumonia (as defined by two or greater occurrences of idiopathic interstitial pneumonia in at least third-degree relatives) between 1999 and 2010. More than 1,700 chest CT scans were available for scoring. Lung tissue samples within 1 year of the CT scan were available for pathologic evaluation in 201 subjects. The tissues were obtained from surgical biopsy, explanted lung, or autopsy (subjects with only transbronchial lung biopsies were excluded).

CT Scan Evaluation

The chest CT scans were scored by two pulmonary radiologists (J. H. C. [6-years experience] and A. C. [8-years experience]). All available chest CT scan images were evaluated. All images of chest CT scans available for a given subject were evaluated by radiologists before scoring. Any discrepancies were resolved by a third pulmonary radiologist (D. A. L.) with approximately 26 years of experience in pulmonary imaging.

Pulmonary fibrosis was defined as reticular abnormality and/or subpleural irregularity or traction bronchiectasis with or without honeycombing. Recorded imaging findings included the presence and extent of reticulation (as a marker for pulmonary fibrosis), honeycombing, and ground-glass opacity as defined by Fleischner glossary of terms²⁵; predominant zonal distribution (upper, mid, lower, diffuse); and predominant axial distribution (peribronchovascular, peripheral, diffuse). The presence of pulmonary fibrosis, honeycombing, and ground-glass opacity was scored on a three-point scale based on level of confidence (none, probable, or definite). The percentage of lung involvement was scored to the nearest 10%.

Readers were allowed to select any combination of diagnoses with level of confidence, including usual interstitial pneumonia, nonspecific interstitial pneumonia, desquamative interstitial pneumonia, respiratory bronchiolitis, organizing pneumonia, acute interstitial pneumonia, hypersensitivity pneumonitis, asbestosis, silicosis, sarcoidosis, obliterative bronchiolitis, and cellular bronchiolitis. In regard to UIP diagnosis, the level of radiologist confidence was separated into four categories: inconsistent with UIP, indeterminate UIP, probable UIP, or definite UIP based on specific criteria (Figs 1-4). Definite UIP was defined as peripheral and basilar predominant pulmonary fibrosis characterized by reticulation, honeycombing, and absence of findings to suggest another specific diagnosis. Probable UIP was defined as peripheral and basilar predominant pulmonary fibrosis with reticulation, little or no honeycombing, and absence of features to suggest another specific diagnosis. Inconsistent with UIP was defined according to the current guidelines.²³ Indeterminate UIP was defined as pulmonary fibrosis with imaging findings not sufficiently characteristic to reach a definite, probable, or inconsistent with UIP level. These were cases in which the CT scan pattern was intermediate between that of probable UIP and

Figure 1 – A-D, Multiple axial images from noncontrast chest CT scan show upper and peripheral predominant pulmonary fibrosis scored as inconsistent with usual interstitial pneumonitis (UIP) based on upper lung preponderance of disease. Incidental note is made of a tracheal bronchus (arrow).

inconsistent with UIP (eg, mild ground-glass opacity slightly more prominent than reticulation, mild-to-moderate degree of air-trapping) or the axial or zonal distribution was diffuse (which is not addressed in current guidelines). Most indeterminate UIP and all probable UIP CT scan classifications used in the current study would be categorized as possible UIP on CT scan according to current guidelines.²³

Histologic Evaluation

Tissue samples were scored by two thoracic pathologists (S. D. G. [10-years experience] and C. D. C. [17-years experience]) with discrepancies resolved by consensus. Scoring of the histologic tissue slides was similar to that of CT scan scoring. Pathologic features were scored as either present, rare, or absent, including temporal heterogeneity, microscopic honeycombing (honeycombing identified on histology), and fibroblastic foci. Each feature was scored only if the pathologists determined that the specimen was of adequate size and resolution to be scored with reasonable confidence, and was otherwise treated as missing data. Diagnoses from pathologic findings were based on recently released guidelines with level of confidence.²⁶ UIP diagnosis was scored

as not considered, possible (<50% likelihood), probable (50%-89% likelihood), or definite ($\geq 90\%$ likelihood). A confident UIP diagnosis required temporal and special heterogeneity with microscopic architectural distortion, usually inclusive of microscopic honeycombing and scar. In addition to UIP diagnosis, any of the idiopathic interstitial pneumonias or secondary causes of pulmonary fibrosis could be selected as diagnostic choices. Level of confidence in diagnosis was mandatory, mirroring the methodology on CT scan.

Genotyping Assay

All subjects with available DNA were genotyped for the *MUC5B* promoter polymorphism (rs35705950). Genotypes of the *MUC5B* SNP were determined using TaqMan genotyping (Life Technologies [Thermo Fisher Scientific Inc]) as previously reported.⁵

Statistical Analysis

χ^2 tests were used to assess associations between groups. A two-tailed Fisher exact test was used in instances where there were expected cell counts less than five, and Monte-Carlo estimates were used to calculate

Figure 2 – A-D, Multiple axial images from noncontrast chest CT scan demonstrates diffuse zonal distribution of mild pulmonary fibrosis as well as mild ground-glass opacity. Ground-glass opacity in most areas is associated with reticulation except for some sparse areas in the upper lung zones (A, B). Due to diffuse zonal distribution of pulmonary fibrosis, this CT scan was scored as indeterminate UIP. Presence of ground-glass opacity slightly above expected given degree of reticulation may have also led to an indeterminate UIP score. See Figure 1 legend for expansion of abbreviation.

Figure 3 – A-D, Multiple axial images from noncontrast chest CT scan show peripheral and basilar predominant pulmonary fibrosis without subpleural honeycombing. This CT scan was scored as probable UIP. See Figure 1 legend for expansion of abbreviation.

P values for tables larger than two $\times$ two. A weighted κ coefficient was used to test for agreement between CT scan and histologic evaluation for assessing honeycombing and diagnosing UIP.²⁷⁻²⁹ The association between the concordance of UIP diagnoses on CT scan and histology

relative to the rs35705950 genotype was also assessed using a Cochran-Armitage trend test. *P* value $< .05$ was considered statistically significant for all tests. All statistical analyses were performed using SAS, version 9.3 (SAS Institute Inc).

Results

The cohort demographics are summarized in Table 1. Average age was 62.9 years $\pm$ 10.2 years. Men comprised 62% of the cohort (125 of 201). Approximately 61% of subjects were former or current smokers. The distribution of genotype at the genetic locus rs35705950 did not

deviate significantly from the expected Hardy-Weinberg equilibrium ($P = .08$): GG 98 (49%), GT 91 (46%), and TT 11 (6%).⁵

There was fair to moderate agreement between readers for CT scan findings (Table 2). The CT scan findings as well as axial and zonal distribution of pulmonary fibrosis

Figure 4 – A-D, Multiple axial images from noncontrast chest CT scan show peripheral and basilar predominant pulmonary fibrosis with subpleural honeycombing consistent with definite UIP. See Figure 1 legend for expansion of abbreviation.

TABLE 1] Demographic and Clinical Characteristics (N = 201)

Characteristic	Value
Sex	
Female	76 (38)
Male	125 (62)
Age at scan, mean (SD), y	62.9 (10.2)
Smoking	
Ever	118 (61)
Never	75 (39)
Genotype (rs35705950)	
GG	98 (49)
GT	91 (46)
TT	11 (6)
Histologic UIP diagnosis	
Not considered	51 (25)
Possible	31 (15)
Probable	44 (22)
Definite	75 (37)
Radiologic UIP diagnosis	
Inconsistent with	70 (35)
Indeterminate	72 (36)
Probable	34 (17)
Definite	25 (12)
Microscopic honeycombing	
Absent	16 (14)
Rare	32 (28)
Present	68 (59)
Honeycombing on CT scan	
None	125 (62)
Probable	17 (8)
Definite	59 (29)
Clinical diagnosis	
Asbestosis	1 (0.5)
Bronchiolitis	1 (0.5)
Desquamative IP	3 (1.5)
Uncharacterized fibrosis	8 (4.0)
Hypersensitivity pneumonitis	3 (1.5)
IPF	109 (54.2)
Nonspecific IP	18 (9.0)
Other ILD	2 (1.0)
Indeterminate/missing	56 (27.9)

Data are given as No. (%) unless otherwise indicated. Not all variables available for all subjects. ILD = interstitial lung disease; IP = interstitial pneumonitis; IPF = idiopathic pulmonary fibrosis; UIP = usual interstitial pneumonitis.

TABLE 2] Agreement Between Readers for CT Scan Findings

Radiology Feature	κ Coefficient (95% CI)	P Value
UIP ^a	0.31 (0.21-0.42)	<.0001
Honeycombing ^a	0.49 (0.38-0.60)	<.0001
Ground-glass ^a	0.39 (0.27-0.52)	<.0001
Zonal distribution ^b	0.24 (0.14-0.35)	<.0001
Axial distribution ^b	0.25 (0.15-0.35)	<.0001

See Table 1 legend for expansion of abbreviation.

^aLinear-weighted κ .

^bSimple κ .

are summarized in Table 3. As expected, given the defined parameters for CT scan UIP diagnosis, 100% of the group with definite UIP had honeycombing (25 of 25), while the inconsistent with UIP group had a far lower proportion of honeycombing (12.9%, nine of 70). The opposite was found for ground-glass opacity. Substantially more ground-glass opacity was seen in inconsistent with UIP group (95.4%, 42 of 44) than those with definite UIP (0.0%, zero of seven) on CT scan. As the confidence for UIP diagnosis increased on CT scan, there was a higher proportion of subjects with a typical distribution for UIP on CT scan (lower lung zone and subpleural predominant pulmonary fibrosis). In regard to histologic results, there was no statistical difference in the proportion of microscopic honeycombing, fibroblastic foci, or temporal heterogeneity across CT scan categories of UIP, though the numbers were small ($P = .09$, $.93$, and $.27$, respectively).

Radiology-Pathology Correlation for Honeycombing and UIP Diagnosis

There was no significant association between CT scan honeycombing and microscopic honeycombing (Fisher exact $P = .76$) (Table 4). In those with CT scan honeycombing, microscopic honeycombing was found in 86.0% of subjects (49 of 57). If honeycombing was not present on CT scan, microscopic honeycombing was still present in 86.4% of subjects (51 of 59). Weighted κ score was -0.005 , 95% CI = $(-0.13, 0.12)$, indicating poor agreement between CT scan and histologic honeycombing.

In regard to concordance of CT scan and histologic UIP scoring (Table 5), the proportions of histologic UIP diagnoses in those with probable vs definite UIP on CT scan ($P = .20$) and in those with inconsistent with vs indeterminate UIP on CT scan ($P = .93$) were not statistically different. However, the proportions of UIP diagnoses on histology in probable UIP vs indeterminate UIP on chest CT scan were statistically different ($P = .01$). In

TABLE 3] Radiologic and Histologic Characteristics by UIP Diagnosis on CT Scan (N = 201)

Features	UIP Diagnosis on CT Scan			
	Inconsistent	Indeterminate	Probable	Definite
Radiologic features				
Honeycombing				
None	61 (87.1)	53 (73.6)	11 (32.4)	0 (0.0)
Probable	2 (2.9)	8 (11.1)	6 (17.7)	1 (4.0)
Definite	7 (10.0)	11 (15.3)	17 (50.0)	24 (96.0)
Ground-glass				
No	2 (4.6)	8 (26.7)	13 (92.9)	7 (100.0)
Probable	5 (11.4)	7 (23.3)	1 (7.1)	0 (0.0)
Definite	37 (84.1)	15 (50.0)	0 (0.0)	0 (0.0)
Percent fibrosis, mean (SD)	25.8 (14.6)	20.7 (10.3)	25.4 (9.7)	33.3 (5.8)
Percent honeycombing, mean (SD)	...	10.0 (0.0)	8.2 (7.5)	16.7 (5.8)
Percent ground-glass, mean (SD)	27.4 (15.5)	17.4 (11.6)	6.7 (5.2)	10.0 (–)
Zonal distribution				
Diffuse	2 (8.3)	8 (40.0)	2 (20.0)	0 (0.0)
Lower	20 (83.3)	10 (50.0)	8 (80.0)	3 (100.0)
Mid	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Upper	2 (8.3)	2 (10.0)	0 (0.0)	0 (0.0)
Axial distribution				
Diffuse	8 (44.4)	11 (68.8)	0 (0.0)	0 (0.0)
PBV	10 (55.6)	0 (0.0)	0 (0.0)	0 (0.0)
Subpleural	0 (0.00)	5 (31.3)	11 (100.0)	3 (100.0)
Histologic features				
Honeycombing				
Absent	5 (14.3)	7 (18.9)	2 (7.7)	2 (11.1)
Rare	16 (45.7)	8 (21.6)	4 (15.4)	4 (22.2)
Present	14 (40.0)	22 (59.5)	20 (76.9)	12 (66.7)
Fibroblastic foci				
Absent	3 (9.1)	3 (10.3)	1 (9.1)	0 (0.0)
Rare	17 (51.5)	13 (44.8)	4 (36.4)	7 (53.9)
Present	13 (39.4)	13 (44.8)	6 (54.6)	6 (46.2)
Temporal heterogeneity				
Absent	9 (16.7)	2 (3.6)	1 (5.6)	0 (0.0)
Rare	16 (29.6)	20 (36.4)	5 (27.8)	6 (33.3)
Present	29 (53.7)	33 (60.0)	12 (66.7)	12 (66.7)

Data are given as No. (%) unless otherwise indicated. Not all variables available for all subjects. PBV = peribronchovascular. See Table 1 legend for expansion of abbreviation.

those with probable UIP on CT scan, 82.4% of subjects (28 of 34) had a probable or definite UIP diagnosis on histology compared with 54.2% of subjects (39 of 72) with indeterminate UIP on CT scan.

UIP Diagnosis Relative to the rs35705950 SNP

There was a significantly higher percentage of subjects with at least one copy of the T allele ($P = .008$) among those with a UIP diagnosis on both histology and on

CT scan (Table 6). Carriage of the T allele was most often associated with a confident UIP diagnosis on CT scan (31 of 51, 61%). The T allele was least often associated with concordant CT scan inconsistent with UIP and histologic not UIP diagnosis (25%).

Discussion

Our study showed that a histologic UIP diagnosis was more often present in subjects with probable UIP on

TABLE 4] Radiologic and Histologic Classification of Honeycombing, Observed (and Expected) Counts

Honeycombing on CT Scan	Microscopic Honeycombing		
	Absent	Rare	Present
None	8 (8.1)	18 (16.3)	33 (34.6)
Probable	0 (1.2)	2 (2.5)	7 (5.3)
Definite	8 (6.6)	12 (13.2)	28 (28.1)

Weighted $\kappa = -0.005$; 95% CI = (-0.13, 0.12); $P = .94$; Fisher exact $P = .76$.

CT scan than indeterminate UIP on CT scan. Our data also show that there is no agreement or association between CT scan honeycombing and microscopic honeycombing, implying that they may represent different structures in the fibrotic lung. Finally, our study also showed that the T allele is associated with a concordant UIP diagnosis on chest CT scan and histology.

Prior studies have indicated a higher likelihood of a histologic UIP diagnosis as the confidence of UIP diagnosis on chest CT scan increases.^{19,22,30-32} Currently, it is suggested that the specificity of a definite CT scan UIP diagnosis is so high that in most cases, lung biopsy is obviated; this is supported by recent guidelines.²³ However, this study indicates that the current guidelines need modification. Under the current guidelines, the indeterminate UIP and probable UIP groups on chest CT scan (as defined in the current study) should be combined into the possible UIP group on chest CT scan. The statistical difference between the histologic scoring of UIP diagnoses in indeterminate CT scan UIP and probable CT scan UIP suggests that these two CT scan groups are different. This suggests that perhaps four levels of UIP diagnosis on chest CT scan are necessary: inconsistent with UIP, indeterminate UIP, probable UIP, and definite UIP. Though we cannot completely rule out a difference in the histologic diagnoses between probable UIP on chest CT scan compared with that of definite UIP on chest CT scan with this sample size, there was no statistical difference between these two groups.

In fact, the percentage of cases of probable UIP on CT scan in which there was a histologic diagnosis of UIP was higher than that of definite UIP on CT scan. Based on this data, it would be tempting to combine the probable UIP with definite UIP groups on chest CT scan for diagnostic purposes. However, given that the main differentiator between these two groups is presence of honeycombing, the two groups may have different prognoses and should be differentiated on imaging unless future studies suggest the contrary.

Honeycombing, as described in the Fleischner Society glossary of terms, is defined as “clustered cystic air spaces, typically of comparable diameters on the order of 3-10 mm.”²⁵ In the setting of pulmonary fibrosis, honeycombing on chest CT scan is important for both diagnostic and prognostic reasons. Honeycombing, in addition to upper lobe subpleural linear opacities, is the most specific finding of UIP on CT scan, and occurs in up to 90% of UIP cases.^{30,33} The extent of honeycombing and of pulmonary fibrosis on CT scan has adverse prognostic ramifications.³³⁻³⁷ Though we hoped to see a relationship between CT scan honeycombing and microscopic honeycombing, there was no such association in our study suggesting that honeycombing on CT scan and histology are dissimilar. It has been shown that CT scan honeycombing is associated with a poor prognosis but this is not the case for microscopic honeycombing; microscopic honeycombing also is not necessarily specific for a UIP diagnosis as opposed to CT scan honeycombing which is highly specific for UIP.³⁸ However, our result should be interpreted cautiously. The resolution of CT scan does not permit recognition of microscopic honeycombing. Additionally, macroscopic CT scan honeycombing may be avoided during surgical lung biopsy.

Prior studies have shown that the minor allele (T) at the *MUC5B* promoter site is associated with IPF and familial pulmonary fibrosis but not with pulmonary fibrosis in the setting of scleroderma (most often non-specific interstitial pneumonitis) or sarcoidosis.^{5,6,10-12}

TABLE 5] Radiologic and Histologic Classification of UIP, Observed (and Expected) Counts

UIP on CT Scan	UIP on Histology			
	Not Considered	Possible	Probable	Definite
Inconsistent	24 (17.8)	11 (10.8)	14 (15.3)	21 (26.1)
Indeterminate	21 (18.3)	12 (11.1)	16 (15.8)	23 (26.9)
Probable	1 (8.6)	5 (5.2)	9 (7.4)	19 (12.7)
Definite	5 (6.3)	3 (3.9)	5 (5.5)	12 (9.3)

Weighted $\kappa = 0.14$; 95% CI = (0.05, 0.22); $P = .0018$; Fisher exact test $P = .03$. See Table 1 legend for expansion of abbreviation.

TABLE 6] rs35705950 Genotype Relative to Radiologic and Histologic Classification of UIP

UIP Diagnosis	GG	GT	TT	GG, %	GT/TT, %
Concordant UIP ^a	18	25	2	40	60
Discordant UIP ^b	20	21	0	49	51
Concordant not UIP ^c	18	6	0	75	25

See Table 1 legend for expansion of abbreviation.

^aConcordant UIP: UIP on CT scan and UIP on histology.

^bDiscordant UIP: (1) UIP on CT scan and not UIP on histology, or (2) inconsistent with UIP on CT scan and UIP on histology.

^cConcordant not UIP: inconsistent with UIP on CT scan and not UIP on histology.

In this study, we showed the association of the T allele with concordant UIP diagnosis on CT scan and histology. Seibold et al⁵ presented three hypotheses on the mechanism accounting for the link between the T allele and IPF. First, the T allele can cause excess production of *MUC5B*, which could conceivably decrease mucosal host defenses. Over time, the cumulative insults to the lung could lead to pulmonary fibrosis. Alternatively, excess *MUC5B* in the small airways could impair alveolar repair either by altering the complex relationship between the type 2 alveolar epithelial cells and the lung matrix or by altering the effectiveness of surfactant. Lastly, the rs35705950 SNP is a putative promoter site for *MUC5B* and may interfere with transcription-factor binding sites. This could lead to ectopic production of *MUC5B* in isolated bronchoalveolar unit, which would help explain why IPF is a spatially heterogeneous process. Our study was not designed to test any of the proposed underlying mechanisms; however, our results do further solidify the association between UIP/IPF and the rs35705950 SNP.

Limitations of this study include the temporal separation of imaging and lung biopsy (up to 1 year). In addition, there was undoubtedly a selection bias given that the majority of the subjects did not have histologic samples for scoring. Most cases of definite UIP on CT scan are no longer biopsied given the high specificity for a UIP/IPF diagnosis with this imaging pattern. Therefore, the subjects in this study likely had more complex or uncertain imaging patterns compared with the full cohort. This could explain the relatively low prevalence of histologic UIP in those with definite UIP on CT scan. Those subjects with a definite CT scan UIP pattern with typical clinical presentation and patient demographics for IPF were likely not biopsied; therefore, subjects in this study with a histologic diagnosis may have presented with clinical manifestations suggestive of an underlying cause for pulmonary fibrosis, prompting biopsy. Furthermore, many of these subjects came from specialized medical centers and were more likely to have complex or atypical disease presentations. In any radiology-pathology study, there is risk of sampling error given that the histologic specimens comprise a very small percentage of total lung volume.

Conclusions

The significant difference between the histology of indeterminate UIP on chest CT scan and probable UIP on chest CT scan suggests that current guidelines (which combine these two groups into the possible UIP category) should separate these groups. Those with probable UIP on CT scan very often have UIP on histology. CT scan and histologic honeycombing are not associated, which implies that they may not be identical entities, though more study is necessary in this regard. The T allele of the rs35705950 SNP is associated with a higher proportion of concordant UIP diagnoses on chest CT scan and histology compared with the G allele.

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