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Common idiopathic pulmonary fibrosis risk variants are associated with hypersensitivity pneumonitis

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Abstract

A subset of patients with hypersensitivity pneumonitis (HP) develop lung fibrosis that is clinically similar to idiopathic pulmonary fibrosis (IPF). To address the aetiological determinants of fibrotic HP, we investigated whether the common IPF genetic risk variants were also relevant in study subjects with fibrotic HP. Our findings indicate that common genetic variants in *TERC*, *DSP*, *MUC5B* and *IVD* were significantly associated with fibrotic HP. These findings provide support for a shared etiology and pathogenesis between fibrotic HP and IPF.

INTRODUCTION

Hypersensitivity pneumonitis (HP) is a cell-mediated diffuse lung disease that results from repeated inhalation of and sensitisation to organic antigens. Fibrotic HP, a subset of HP, is clinically similar to idiopathic pulmonary fibrosis (IPF) and is thought to be influenced by persistent exposure to a causative protein. Although previous candidate gene studies in HP have found that HLA molecules involved in the processing and presentation of antigens are involved in the aetiology of HP,[1] it remains unknown why only certain individuals exposed to organic antigens develop HP, and only a subset of HP cases develop lung fibrosis. Recently, IPF-related genes including rare telomere variants and the *MUC5B* promoter

variant rs35705950 were also identified as risk variants for HP, especially in cases with fibrosis.[2 3] In addition to *MUC5B*, genome-wide association studies (GWAS) have identified several common variants that influence the risk of developing IPF.[4 5] The purpose of this study is to determine whether common variants identified in our IPF GWAS[6] and validated by resequencing[4] are genetically relevant in patients with HP, and whether there were specific IPF genetic variants associated with fibrotic HP.

METHODS

Study participants

We conducted a retrospective case–control study that includes non-Hispanic white HP participants (N=226) enrolled at National Jewish Health (72 cases), University of California San Francisco (72 cases), the Lung Tissue Research Consortium (79 cases) and Royal Brompton Hospital (3 cases). Each institution or consortia made the diagnosis of HP according to accepted guidelines or by multidisciplinary consensus using the American College of Chest Physicians (ACCP) and American Thoracic Society (ATS) criteria.[7 8] Presence or absence of fibrosis was defined as evidence of honeycombing with/or traction bronchiectasis on CT scan, and/or honeycombing with/or fibrosis on pathological review. The unaffected control subjects were selected from participants enrolled in the COPD Gene Study that had self-reported as non-Hispanic white.[4]

Candidate single-nucleotide polymorphism genotyping

HP cases were genotyped for the 10 common IPF genetic variants including *TERC* (rs2293607), *FAM13A* (rs2609260), *TERT* (rs7726159), *DSP* (rs2076295), *ZKSCAN1* (rs6963345), *OBFC1* (rs2488000), *MUC5B* (rs35705950), *ATP11A* (rs1278769), *IVD* (rs35700143) and *DPP9* (rs12610495) using Viaa7 real-time PCR system (Applied Biosystems, Foster City, California, USA) as previously reported.[4]

Statistical analyses

Logistic regression analyses were performed to test each common variant for association with HP compared with control subjects, allowing for adjustment of relevant covariates and evaluation of the minor allele frequencies and OR. An additive genetic model was used for each variant. Given that this is a hypothesis-driven study, with candidate single nucleotide polymorphisms (SNPs) being chosen based on strong evidence for association with other interstitial lung diseases, significance was assessed using the Benjamini-Hochberg procedure to control the false discovery rate at a level of 5%. In secondary analyses, logistic regression analysis for each common variant was performed in subsets of HP subjects defined by the radiographic or histological presence of lung fibrosis. We also included all 10 common variants in a single logistic regression model to assess the independent effects of the variants on fibrotic HP. Finally, we used a proportional odds model to test the association between *MUC5B* and the gender, age, physiology (GAP) index.[9] The effect of sex as a potential covariate was assessed in all models. The statistical analyses were performed using R and JMP Pro V.15.0.0 (SAS).

RESULTS

Clinical features of enrolled subjects

Table 1 shows the clinical characteristics of 226 cases with HP and 1355 controls included in this study. There was no significant difference in sex between the two groups, whereas age was older (61.2±10.4 vs 59.2±10.0, p=0.0005) and smoking history was reduced (54% vs 86%, p<0.0001) in HP subjects compared with control subjects. GAP index was evaluated based on gender, age, and pulmonary function.[9] Of 148 cases with HP with pulmonary function data (table 1), 89 subjects were identified as stage I, 49 subjects stage II, and 10 subjects stage III. Fibrotic HP subjects showed lower pulmonary function when compared with non-fibrotic subjects (table 2).

Genetic variants associated with HP

Six of the 10 common IPF risk variants were significantly associated with HP, independent of sex (table 3). All 10 variants had a consistent direction of risk effect between HP and those reported for IPF.[4] The *MUC5B* promoter variant rs35705950 showed the strongest association with HP compared with control subjects (OR; 2.11, p=1.7×10^{-6}). In addition, common variants in *TERC*, *FAM13A*, *DSP*, *ATP11A*, and *IVD* were also associated with HP. Among subjects with HP, 152 subjects had radiographic or histological evidence of lung fibrosis and 47 subjects demonstrated no evidence of lung fibrosis. Analysing the common IPF risk variants in patients with fibrotic HP, we found that *TERC*, *DSP*, *MUC5B*, and *IVD* were significantly associated with this subgroup of fibrotic HP patients. After including all variants in a single model of fibrotic HP, *TERC*, *MUC5B* and *IVD* remained statistically significant, while *DSP* was only moderately associated (OR; 1.24, p=0.10) with fibrotic HP (table 3). In contrast, non-fibrotic HP was associated with variants in *OBFC1*. In evaluating the utility of the GAP index, we found that the *MUC5B* promoter variant rs35705950 was significantly associated with a higher GAP index (OR; 2.3, p=4.8×10^{-3}).

DISCUSSION

Our findings indicate that the common IPF risk variants also represent risk variants for HP, especially fibrotic HP. Similar to what was reported previously, the *MUC5B* promoter variant rs35705950 is most strongly associated with HP.[3] We also found that the *MUC5B* promoter variant is strongly associated with fibrotic HP but not non-fibrotic HP and is indicative of more severe physiologic changes. Others have reported that the *MUC5B* risk allele is associated with a more confident usual interstitial pneumonia (UIP) pattern in patients with IPF,[10] and with UIP-like CT findings in HP,[3] rheumatoid arthritis[11] and asbestosis.[12 13] These results suggest that *MUC5B* may prove to be a generalised risk factor for fibrosing lung diseases, especially those with a UIP pattern.

In addition to the *MUC5B* promoter variant, *ATP11A*, *DSP*, *TERC*, *FAM13A* and *IVD* were also associated with HP. These results indicate that multiple genes play a role to development of HP, including host defence (*MUC5B*, *ATP11A*), cell-cell adhesion (*DSP*), telomere length maintenance (*TERC)* and other functions (*FAM13A*, *IVD*). Among the six genes associated with HP, *MUC5B*, *DSP*, *IVD* and *TERC* were also associated with fibrotic

HP. *DSP* is a desmosomal protein that is critical to cell–cell adhesion. *DSP* expression is higher in the IPF lung when compared with control subjects, and rs2076295 is strongly associated with IPF.[14] Hao *et al* reported that human bronchial epithelial cells (HBEC) with the *DSP* risk allele had a lower expression of *DSP* compared with the common genotype, and reduced levels of *DSP* in HBEC promoted cell migration, led to epithelial-mesenchymal transition and fibrosis.[15] The results presented in the current analysis extend these findings and demonstrate the importance of the *DSP* risk variant rs2076295 in HP, especially those with fibrotic HP. Variants in *FAM13A* have been found in GWAS to associate with various lung diseases including COPD, asthma and idiopathic interstitial pneumonias. IPF and COPD shared their risk allele in *FAM13A*, however, the risk allele has opposite effects between these diseases.[16] [17] *OBFC1*, was associated with non-fibrotic HP but not with fibrotic HP and showed a consistent direction of risk effect with IPF. It is unclear why this SNP was associated with non-fibrotic HP, but not fibrotic HP, and should be explored in future studies.

There are several limitations with this study. First, while this is one of the largest cohort for genetic analysis with HP subjects, the number of subjects in this study is relatively small, especially with non-fibrotic HP. Therefore, it is difficult to interpret the positive or negative findings in this sub-cohort. Second, as this is a cross-sectional study, we could not assess the differences in time since diagnosis between groups or the time-course of disease. Third, while the analysis included subjects from multiple cohorts, the data were combined into a single dataset for analysis and there is no replication cohort due to sample size. Further examination with a larger and prospective study may be warranted. Fourth, the diagnosis of HP was not made centrally, but was made by accepted guidelines or by multidisciplinary consensus using the ACCP or ATS criteria. Finally, we cannot fully exclude the possibility of some misdiagnosis between IPF and HP in this study or previous studies of IPF given the considerable diagnostic overlap.

In aggregate, these findings provide further support that fibrotic HP is influenced by common IPF risk alleles, and suggests that IPF and fibrotic HP may share a common etiology and pathogenesis.

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Competing interests

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Table 1

Clinical characteristics of HP subjects and controls

	HP (%)	Control (%)	P value
Subjects	226	1355	
Sex (male/female)	92 (41)/134 (59)	570 (42)/785 (58)	0.7
Age	61.2±10.4	59.2±10.0	0.0005
Smoking history (ever/never)	117 (54)/100 (46)	1170 (86)/175 (14)	<0.0001
Pulmonary function			
%FVC (N=167)	65.5±21.5	NA	
%DLco (N=150)	52.2±20.5	NA	
GAP index (N=148)			
Stage1	89 (60)	NA	
Stage2	49 (33)	NA	
Stage3	10 (7)	NA	
Fibrosis (yes/no/unknown)	152 (67) /47 (21)/27 (12)	NA	
CT-proven fibrosis (yes/no/unknown)	120 (53)/8 (4)/98 (43)	NA	
Pathology proven fibrosis (yes/no/unknown)	77 (34)/47 (21)/102 (45)	NA	
Antigen identification (yes/no/unknown)	124 (55)/51 (23)/51 (23)	NA	

%DLco, diffusing capacity of the lung for carbon monoxide, % of predicted value; %FVC, forced vital capacity, % of predicted value; HP, hypersensitivity pneumonitis; NA, not available.

Table 2

Clinical characteristics of HP

	Fibrotic HP (%)	Non-fibrotic HP (%)	P value
Subjects	152	47	
Sex (male/female)	66 (43)/86(57)	16(34)/31(66)	0.25
Age	62.0±10.1	59.4±9.6	0.09
Smoking History (ever/never)	86 (57)/64(42)	21(45)/26(55)	0.13
Antigen identification (yes/no/unknown)	97 (63)/40 (26)/15(10)	22(47)/9 (19)/16(34)	0.99
Pulmonary function			
%FVC	62.6±21.7	76.8±16.7	0.0005
%Dlco	50.3±20.4	61.0+18.8	0.008

%DLco, diffusing capacity of the lung for carbon monoxide, % of predicted value; %FVC, forced vital capacity, % of predicted value; HP, hypersensitivity pneumonitis.

Table 3

Association of candidate gene variants with HP

CHR	Gene	SNP	All HP		Fibrotic HP		Non-fibrotic HP		Full model* (fibrotic HP)	
			OR	Adjusted P value	OR	Adjusted P value	OR	Adjusted P value	OR	P value
3	TERC	rs2293607	1.31	0.04	1.42	0.03	1.04	0.97	1.37	0.04
4	FAM13A	rs2609260	1.35	0.04	1.29	0.19	1.63	0.15	1.29	0.13
5	TERT	rs7726159	0.88	0.27	0.82	0.21	1.01	0.97	0.85	0.26
6	DSP	rs2076295	1.35	0.02	1.37	0.03	1.31	0.43	1.24	0.10
7	ZKSCAN1	rs6963345	1.22	0.08	1.07	0.60	1.38	0.35	1.17	0.26
10	OBFC1	rs2488000	1.22	0.27	0.87	0.60	2.32	0.02	0.85	0.48
11	MUC5B	rs35705950	2.11	1.74E-06	2.32	2.61E-06	1.02	0.97	2.26	3.56E-06
13	ATP11A	rs1278769	0.72	0.04	0.81	0.21	0.46	0.06	0.81	0.19
15	IVD	rs35700143	0.78	0.04	0.66	0.01	1.17	0.81	0.68	0.01
19	DPP9	rs12610495	0.94	0.56	0.82	0.21	1.01	0.97	0.72	0.03

*
Full model includes all 10 variants in a single logistic regression.

CHR, chromosome; HP, hypersensitivity pneumonitis; SNP, single nucleotide polymorphism.