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A Variant in the Promoter of *MUC5B* and Idiopathic Pulmonary Fibrosis

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To the Editor

Idiopathic pulmonary fibrosis is a complex genetic disease; mutations in surfactant protein C, telomerase, and surfactant protein A2 have been identified in familial cases of pulmonary fibrosis.[1,2] We confirm a recent association with rs35705950 in the putative promoter of *MUC5B* and sporadic idiopathic pulmonary fibrosis.[3]

Patients with idiopathic pulmonary fibrosis were recruited independently from the Simmons Center for Interstitial Lung Diseases at the University of Pittsburgh Medical Center between 2003 and 2010 and from the Interstitial Lung Disease Center at the University of Chicago between 2006 and 2009. Our study was approved by the institutional review boards of both universities, and patients provided written informed consent for participation. The diagnosis of idiopathic pulmonary fibrosis was based on clinical, physiological, and high-resolution computed tomographic findings in accordance with criteria of the American Thoracic Society and the European Respiratory Society[4]; the diagnosis was based on surgical lung-biopsy results in 44.2% of the Chicago cohort and 53.7% of the Pittsburgh cohort. Patients with known causes of interstitial lung disease were excluded. The controls, who were randomly recruited from the two medical centers, were healthy subjects who did not have lung diseases. Only non-Hispanic whites in the United States were included. The rs35705950 single-nucleotide polymorphism (SNP) was genotyped with the use of a TaqMan assay and an ABI 7900 HT DNA analyzer (Applied Biosystems) with genomic DNA.

The demographic and clinical characteristics of the subjects are summarized in Table 1. Case–control analysis showed significant allelic and genotypic associations of the rs35705950 SNP with idiopathic pulmonary fibrosis in both the Pittsburgh and the Chicago

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cohorts (Table 1). The minor-allele frequency in the combined cohort was 34.3% in patients with idiopathic pulmonary fibrosis and 11.1% in controls (allelic association, $P=7.6\times10^{-40}$). The odds ratios for idiopathic pulmonary fibrosis in subjects who were heterozygous or homozygous for the minor allele of rs35705950 were 5.9 (95% confidence interval, [CI], 4.4 to 7.8) and 9.7 (95% CI, 4.7 to 19.9), respectively (Table 1).

The significant association of the rs35705950T variant with idiopathic pulmonary fibrosis in two independent cohorts suggests that MUC5B, a gel-forming mucin expressed by bronchial epithelial cells and generally associated with chronic airway disease,[5] may have a major role in the pathobiology of idiopathic pulmonary fibrosis. Further study of MUC5B regulation and the downstream influences of MUC5B on lung responses to injury may result in better understanding of the mechanism of the lung phenotype in idiopathic pulmonary fibrosis as well as improved tools for diagnosis and management.

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References

1. Nogee LM, Dunbar AE III, Wert SE, Askin F, Hamvas A, Whitsett JA. A mutation in the surfactant protein C gene associated with familial interstitial lung disease. N Engl J Med. 2001; 344:573–579. [PubMed: 11207353]
2. Wang Y, Kuan PJ, Xing C, et al. Genetic defects in surfactant protein A2 are associated with pulmonary fibrosis and lung cancer. Am J Hum Genet. 2009; 84:52–59. [PubMed: 19100526]
3. Seibold MA, Wise AL, Speer MC, et al. A common MUC5B promoter polymorphism and pulmonary fibrosis. N Engl J Med. 2011; 364:1503–1512. [PubMed: 21506741]
4. Demedts M, Costabel UA. TS/ERS international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Eur Respir J. 2002; 19:794–796. [PubMed: 12030715]
5. Kamio K, Matsushita I, Hijikata M, et al. Promoter analysis and aberrant expression of the MUC5b gene in diffuse panbronchiolitis. Am J Respir Crit Care Med. 2005; 171:949–957. [PubMed: 15709052]

Table 1

Characteristics of the Subjects.*

Variable	University of Pittsburgh			University of Chicago			Overall		
	Cases (N=246)	Controls (N=166)	P Value	Cases (N=95)	Controls (N=636)	P Value	Cases (N=341)	Controls (N=802)	P Value
Male sex — no. (%)	163 (66.3)	71 (42.8)		75 (78.9)	365 (57.4)		238 (69.8)	436 (54.4)	
Age — yr	67.4±9.0	48.7±16.1		69.2±8.4	53.7±14.1		67.9±8.8	52.7±14.7	
FVC — % of predicted value†	62.4±18.8	NA		65.0±19.8	NA		63.1±19.1	NA	
DLCO — % of predicted value‡	44.9±18.2	NA		47.0±18.3	NA		45.4±18.2	NA	
Minorallele(T)—%	33.7	10.8	6.7×10^{-14}	35.8	11.2	1.8×10^{-14}	34.3	11.1	7.6×10^{-40}
Genotype — no. (%)			2.3×10^{-15}			1.0×10^{-17}			1.5×10^{-40}
GG	95 (38.6)	132 (79.5)		36 (37.9)	504 (79.2)		131 (38.4)	636 (79.3)	
GT	136 (55.3)	32 (19.3)		50 (52.6)	122 (19.2)		186 (54.6)	154 (19.2)	
TT	15 (6.1)	2 (1.2)		9 (9.5)	10 (1.6)		24 (7.0)	12 (1.5)	
Odds ratio (95% CI)									
GT vs. GG	5.9 (3.7–9.4)			5.7 (3.6–9.2)	5.9 (4.4–7.8)				
TT vs. GG	10.4 (2.3–6.6)	12.6 (4.8–33.0)		9.7 (4.7–19.9)					
P value for Hardy-Weinberg equilibrium	0.001	0.97		0.16	0.41		0.001	0.45	

*Plus-minus values are means ±SD. CI denotes confidence interval, DLCO diffusion capacity of carbon monoxide, FVC forced vital capacity, and NA not applicable.

†Calculations are based on 238, 91, and 329 subjects in the Pittsburgh, Chicago, and overall cohorts, respectively.

‡Calculations are based on 230, 83, and 313 subjects in the Pittsburgh, Chicago and overall cohorts, respectively.