

ORIGINAL ARTICLE

MUC5B Promoter Polymorphism and Interstitial Lung Abnormalities

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ABSTRACT

BACKGROUND

A common promoter polymorphism (rs35705950) in *MUC5B*, the gene encoding mucin 5B, is associated with idiopathic pulmonary fibrosis. It is not known whether this polymorphism is associated with interstitial lung disease in the general population.

METHODS

We performed a blinded assessment of interstitial lung abnormalities detected in 2633 participants in the Framingham Heart Study by means of volumetric chest computed tomography (CT). We evaluated the relationship between the abnormalities and the genotype at the rs35705950 locus.

RESULTS

Of the 2633 chest CT scans that were evaluated, interstitial lung abnormalities were present in 177 (7%). Participants with such abnormalities were more likely to have shortness of breath and chronic cough and reduced measures of total lung and diffusion capacity, as compared with participants without such abnormalities. After adjustment for covariates, for each copy of the minor rs35705950 allele, the odds of interstitial lung abnormalities were 2.8 times greater (95% confidence interval [CI], 2.0 to 3.9; $P < 0.001$), and the odds of definite CT evidence of pulmonary fibrosis were 6.3 times greater (95% CI, 3.1 to 12.7; $P < 0.001$). Although the evidence of an association between the *MUC5B* genotype and interstitial lung abnormalities was greater among participants who were older than 50 years of age, a history of cigarette smoking did not appear to influence the association.

CONCLUSIONS

The *MUC5B* promoter polymorphism was found to be associated with interstitial lung disease in the general population. Although this association was more apparent in older persons, it did not appear to be influenced by cigarette smoking. (Funded by the National Institutes of Health and others; ClinicalTrials.gov number, NCT00005121.)

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SUBCLINICAL INTERSTITIAL LUNG ABNORMALITIES are relatively common findings on imaging studies in smokers and elderly persons.¹ Accumulating evidence suggests that these abnormalities may precede the development of clinically relevant pulmonary fibrosis.¹⁻⁷ However, it is not known whether there is a genetic association between interstitial lung abnormalities and pulmonary fibrosis in the general population.

Recently, a single-nucleotide polymorphism (SNP) (rs35705950) in the promoter of the gene encoding mucin 5B (*MUC5B*) was shown to be associated with both familial interstitial pneumonia and sporadic idiopathic pulmonary fibrosis.⁸ In addition, the *MUC5B* variant was associated with increased expression of *MUC5B* in the lungs of controls, and *MUC5B* transcript levels were elevated in the lungs of patients with idiopathic pulmonary fibrosis, as compared with controls.⁸ The data suggest that the *MUC5B* variant conferring an increased risk of pulmonary fibrosis is common, since the minor allele of rs35705950 is present in approximately 20% of the European CEPH (Centre d'Etude du Polymorphisme Humain) population in the 1000 Genomes Project.⁹ In addition, the *MUC5B* variant has been observed more frequently both in patients with familial and in those with sporadic forms of pulmonary fibrosis than in adults without pulmonary fibrosis, and the presence of the variant has been associated with an increase by a factor of 8 in the risk of sporadic idiopathic pulmonary fibrosis.⁸

On the basis of these findings, we hypothesized that persons with the *MUC5B* variant in the general population would have an increased prevalence of interstitial lung disease. To test this hypothesis, we assessed chest scans obtained on volumetric computed tomography (CT) performed as part of the Framingham Heart Study. On the basis of known risk factors for pulmonary fibrosis,¹⁰ in the Multidetector Computed Tomography 2 (FHS-MDCT2) study, we additionally evaluated the relationship between the *MUC5B* polymorphism and interstitial lung abnormalities for a modification of effect according to age and smoking status.

METHODS

STUDY DESIGN

The Framingham Heart Study, which was initiated in 1948, is a longitudinal study that was originally designed to identify epidemiologic risk factors for cardiovascular disease. There are now multiple cohorts from the study with a wide range of phenotypic data.¹¹ In our study, we evaluated data for 2764 adult men and women from the third-generation and offspring cohorts, comprising mostly non-Hispanic white participants. Research phenotypes that have been assessed in this cohort included a physical examination; measurement of spirometry and diffusion capacity of carbon monoxide, as measured on the Collins Classic Pulmonary Function Laboratory system (Ferraris Respiratory); respiratory questionnaires^{12,13}; blood-sample collection; and volumetric, inspiratory, and thoracic chest CT, as performed with the 64-slice positron-emission tomography (PET)-CT Discovery VCT scanner (GE Healthcare).

The study was approved by the institutional review boards at Boston University and Brigham and Women's Hospital. All participants provided written informed consent, including consent for the use of their DNA in genetic studies.

GENOTYPING AND THORACIC CHEST CT ANALYSIS

Genotyping of the putative promoter polymorphism in *MUC5B* (rs35705950) was performed with the use of Taqman Genotyping Assays (Applied Biosystems), as described previously.⁸ Chest CTs were evaluated by three readers (including two chest radiologists and one pulmonologist) using a VirtualPlace workstation (AZE) and a sequential reading method, as described previously.^{1,7,14} (Details are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.) Interstitial lung abnormalities were defined as nondependent changes affecting more than 5% of any lung zone, including ground-glass or reticular abnormalities, diffuse centrilobular nodularity, nonemphysematous cysts, honeycombing, or traction bronchiectasis (Fig. 1A and 1C). CT images showing either focal or unilateral ground-glass attenuation, fo-

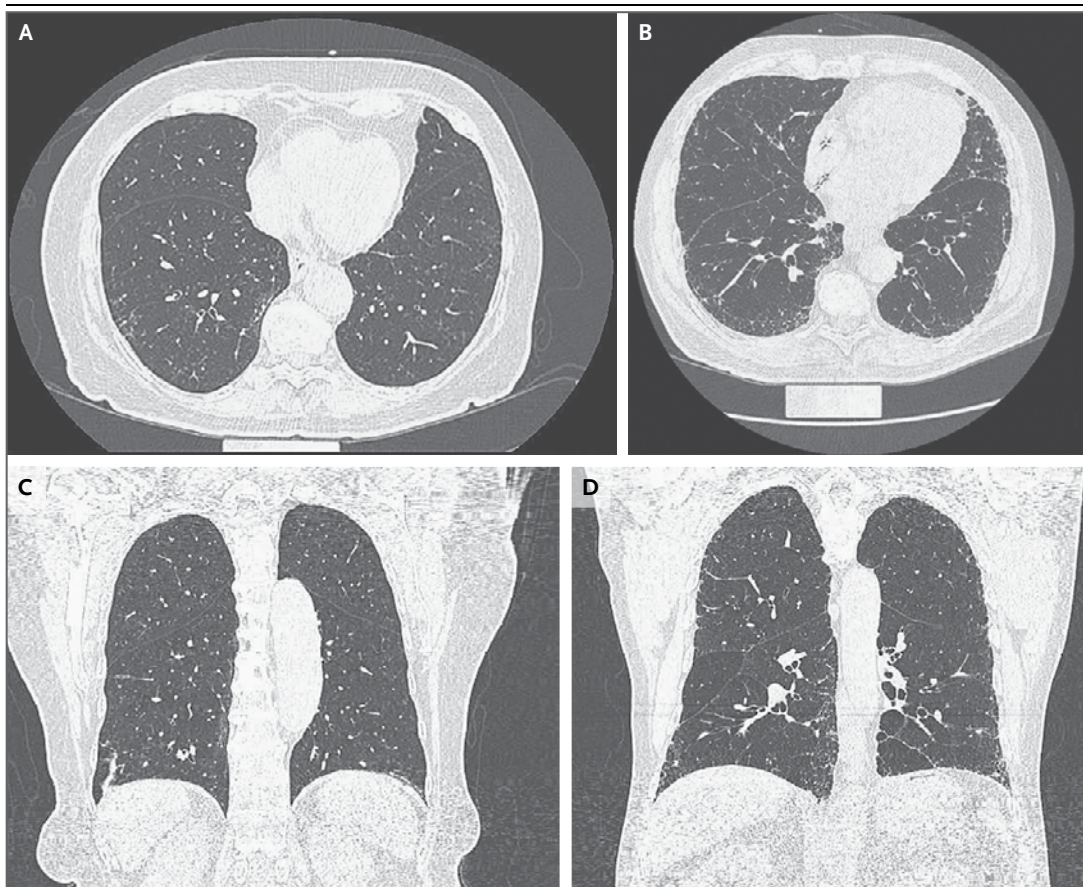


Figure 1. Computed Tomographic Images of Two Participants with Lung Abnormalities.

Shown are axial images (Panels A and B) and coronal images (Panels C and D) obtained from two participants in the Framingham Heart Study. Panels A and C (Participant 1) show representative features of interstitial lung abnormalities, and Panels B and D (Participant 2) show pulmonary parenchymal architectural distortion highly suggestive of a fibrotic lung disease (definite fibrosis).

cal or unilateral reticulation, or patchy ground-glass abnormality (<5% of the lung) were considered to be indeterminate. To assess the association between *MUC5B* genotype and pulmonary fibrosis, we created an additional subset of interstitial lung abnormalities that were limited to persons with pulmonary parenchymal architectural distortion highly suggestive of a fibrotic lung disease (definite fibrosis)¹⁵ (Fig. 1B and 1D). All qualitative CT assessments and subtyping of lung abnormalities were performed by a consensus of three readers who were unaware of additional participant-specific information. Quantitative measures of total lung capacity were performed with the use of Airway Inspector (www.airwayinspector.org), an open-source tool

for CT-based image quantitative analysis of the lung, as described previously.¹⁶

STATISTICAL ANALYSIS

All analyses accounted for familial relationships in the Framingham Heart Study with the use of generalized linear models, as described previously,¹⁷ and were adjusted for covariates including age, sex, body-mass index, and smoking behavior, as indicated. All genetic analyses were performed with the use of an additive genetic model.⁸ We performed interaction tests to evaluate whether age, lung-abnormality subtype, or smoking status modified the associations between the *MUC5B* genotype and lung abnormalities. Reported P values are two-sided, and P val-

ues of less than 0.05 were considered to indicate statistical significance.

RESULTS

THORACIC CT SCANS

Of the 2764 participants, 2633 (95%) had both genotypic data and a thoracic CT available and were included in this analysis. Of the 2633 CT scans that were evaluated, 177 (7%) showed interstitial lung abnormalities, 1086 (41%) were indeterminate, and 1370 (52%) did not have lung abnormalities (Table 1 and Fig. 2).¹⁸⁻²⁰ Of the 1320 CT scans that were scored by at least two readers, 902 (68%) were concordant. Of the 418 discordant reads, 399 (95%) involved 1 indeterminate read, whereas a discrepancy between the presence or absence of lung abnormalities occurred in 19 participants (5%).

LUNG ABNORMALITIES AND CHARACTERISTICS OF PARTICIPANTS

Baseline characteristics, along with comparisons between study participants with interstitial lung abnormalities, those with indeterminate abnormalities, and those without such abnormalities, are shown in Table 1. As compared with participants without interstitial lung abnormalities, those who were found to have such abnormalities were older, had increased exposure to tobacco smoke, and were more likely to report having a chronic cough and shortness of breath.

Although no major differences in spirometric measures were noted among the three groups, participants with interstitial lung abnormalities had reduced measures of the diffusion capacity of carbon monoxide and total lung capacity, as compared with those without such abnormalities. For example, participants with lung abnormalities were about twice as likely as those without abnormalities to report having a cough and shortness of breath. They also had relative reductions of 12% in the mean diffusion capacity of carbon monoxide and 9% in total lung capacity (with both measures as a percent of the predicted value). More than half the participants with interstitial lung abnormalities had a CT-measured total lung capacity of less than 80% of the predicted value, a finding that was consistent with a restrictive lung deficit.²⁰

MUC5B GENOTYPE AND LUNG ABNORMALITIES

The minor allele frequency of the *MUC5B* promoter SNP (rs3570950) was 10.5%, and this SNP was in Hardy–Weinberg equilibrium in the Framingham Heart Study. The prevalence of lung-abnormality status according to genotypic category is presented in Figure 2. For each copy of the *MUC5B* variant, there was an increase in the percentage of the population that had interstitial lung abnormalities. In the Framingham Heart Study, there was an association between *MUC5B* genotype and interstitial lung abnormalities in adjusted models that accounted for familial relationships and for additional covariates (Table 2). For example, after adjustment for covariates, for each copy of the *MUC5B* variant, the odds of lung abnormalities were 2.8 times greater, as compared with those with the major *MUC5B* allele (Table 2). Of note, there was no significant association between the presence of the *MUC5B* variant and a scan that was indeterminate for interstitial lung abnormalities (odds ratio, 1.1; 95% confidence interval [CI], 0.9 to 1.3; $P=0.44$) (data not shown).

MUC5B GENOTYPE, LUNG ABNORMALITIES, AND AGE

There was strong evidence that age was associated with interstitial lung abnormalities (Table 1). For example, the prevalence of interstitial lung abnormalities in participants who were 50 years of age or younger was 2%. In contrast, the prevalence of such abnormalities in study participants over the age of 50 years was 9% (Fig. 2). Although there was not strong evidence that age modified the association between *MUC5B* and interstitial lung abnormalities ($P=0.10$), on the basis of these findings, we evaluated the associations between the *MUC5B* genotype and interstitial lung abnormalities stratified according to age. Although there was no evidence for an association between *MUC5B* and interstitial lung abnormalities among participants 50 years of age or younger (odds ratio, 1.1; 95% CI, 0.2 to 4.8; $P=0.95$), among those more than 50 years of age, for each copy of the *MUC5B* variant, there was more than double odds of having interstitial lung abnormalities (odds ratio, 2.5; 95% CI, 1.7 to 3.5; $P<0.001$).

MUC5B GENOTYPE AND INTERSTITIAL SUBTYPE

Of the 177 participants with interstitial lung abnormalities (Fig. 1), 5 were noted to have

Table 1. Baseline Characteristics of the Participants, According to the Status of Interstitial Lung Abnormalities (ILA).*

Characteristic	Participants without ILA (N=1370)	Participants with Indeterminate ILA (N=1086)	Participants with ILA (N=177)	P Value	
				All Groups	ILA vs. No ILA†
Age — yr	56±11	61±12	70±12	<0.001	<0.001
Female sex — no. (%)	675 (49)	561 (52)	89 (50)	0.48	0.81
Body-mass index	29±6	28±5	28±5	0.08	0.59
Smoking status					
Former smoker — no./total no. (%)	591/1360 (43)	501/1073 (47)	92/175 (53)	0.06	0.03
Current smoker — no./total no. (%)	73/1360 (5)	72/1073 (7)	17/175 (10)	0.09	0.04
Pack-yr — no.	17±16	21±20	26±20	<0.001	<0.001
Respiratory symptoms — no. (%)					
Chronic cough	87 (6)	68 (6)	21 (12)	0.02	0.006
Shortness of breath with minor exertion	117 (9)	143 (13)	31 (18)	<0.001	<0.001
Pulmonary-function testing					
FEV ₁ — % of predicted value‡	98±15	98±15	98±17	0.67	0.65
FVC — % of predicted value‡	101±13	103±13	101±15	0.03	0.90
FEV ₁ :FVC — % of predicted value‡	96±9	95±9	97±9	0.03	0.31
Spirometric restriction — no./total no. (%)§	48/1297 (4)	25/1011 (2)	6/159 (4)	0.25	0.96
Airflow obstruction — no./total no. (%)¶	59/1297 (5)	54/1011 (5)	10/159 (6)	0.48	0.31
Diffusion capacity of carbon monoxide — % of predicted value	98±15	97±15	86±14	<0.001	<0.001
Total lung capacity**					
Mean — liters	5.2±1.2	4.7±1.1	4.6±1.2	<0.001	<0.001
Percent of predicted value	88±14	80±16	79±17	<0.001	<0.001
<80% of predicted value — no./total no. (%)	359/1299 (28)	483/981 (49)	81/148 (55)	<0.001	<0.001

* Plus–minus values are means ±SD. Data are missing for patients in the following categories: current and former smoking status, 25 participants (1%); spirometry, 165 participants (6%); diffusion capacity of carbon monoxide, 572 participants (22%); and total lung capacity, 192 participants (7%). The body-mass index is the weight in kilograms divided by the square of the height in meters. FEV₁ denotes forced expiratory volume in 1 second, and FVC forced vital capacity.

† P values for the comparison among all groups and for the comparison between participants with ILA and those without ILA were calculated with the use of general linear models to account for familial relationships in the Framingham Heart Study, as described previously.¹⁷

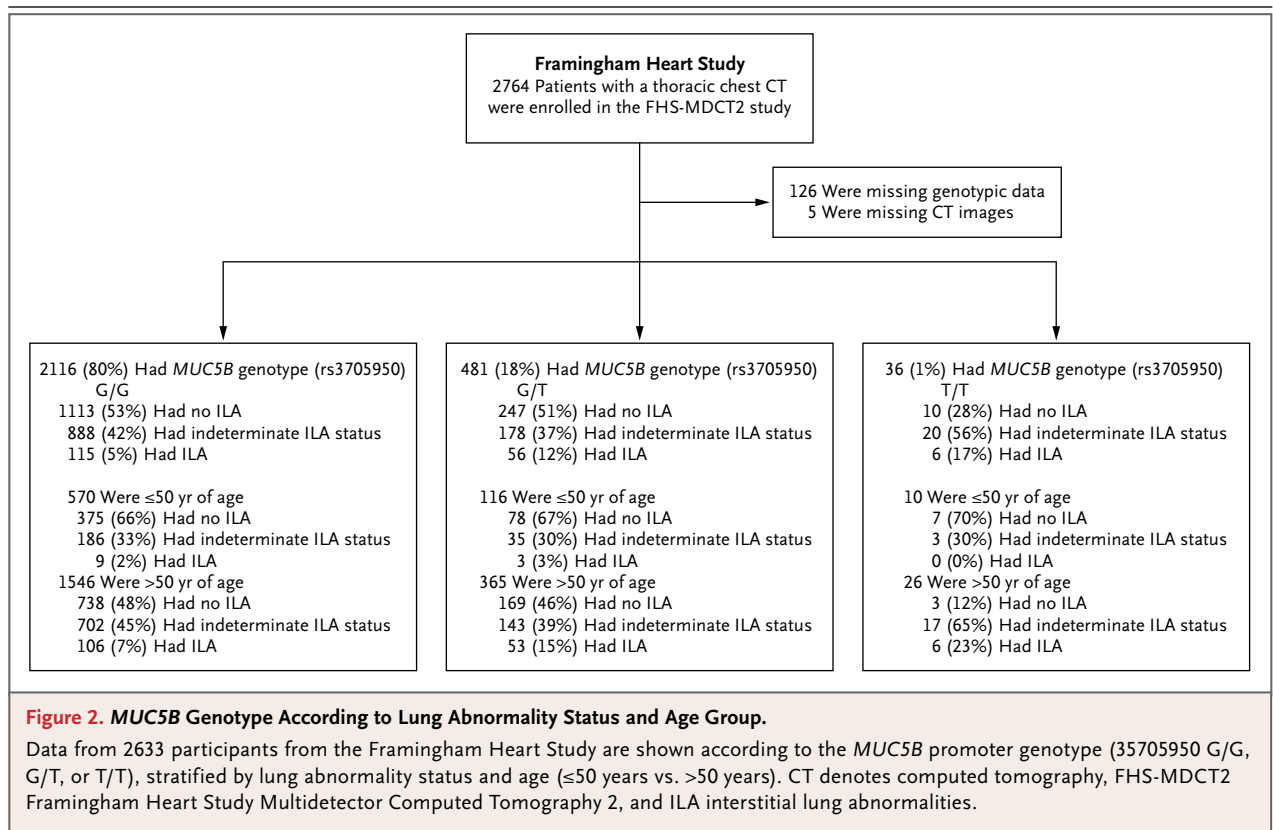
‡ Predicted values for FEV₁ and FVC are derived from Hankinson et al.¹⁸

§ Spirometric restriction was defined as an FVC of less than 80% of the predicted value with an FEV₁:FVC ratio that is more than the lower limit of the normal range.¹⁸

¶ Airflow obstruction was defined as an FEV₁ and an FEV₁:FVC ratio that are both less than the lower limit of the normal range.¹⁸

|| Predicted values for the diffusion capacity of carbon monoxide are derived from Miller et al.¹⁹

** Quantitative values for total lung capacity were calculated with the use of Airway Inspector (www.airwayinspector.org). Predicted values in this category are based on the guidelines of the American Thoracic Society and European Respiratory Society.²⁰



extensive calcified pleural plaques strongly suggestive of asbestos exposure (Fig. S1 in the Supplementary Appendix).²¹ There was no decrement in the association between the MUC5B variant and interstitial lung abnormalities after removal of the 5 participants with pleural plaques. For each copy of the MUC5B variant, participants had more than double the odds of having interstitial lung abnormalities (odds ratio, 2.7; 95% CI, 1.9 to 3.8; $P < 0.001$). Of the 5 participants with extensive pleural plaques, 2 (40%) had at least one copy of the MUC5B variant.

Of the 177 participants with interstitial lung abnormalities, 47 (27%) could be further classified as having definite CT evidence of pulmonary fibrosis (Fig. 1B and 1D). Baseline characteristics of all the participants with lung abnormalities as compared with those of patients with definite fibrosis are presented in Table S1 in the Supplementary Appendix. After adjustment for covariates, for each copy of the MUC5B variant, the odds of definite fibrosis were

6.3 times greater (Table 2). Despite these findings, there was no evidence that the association between MUC5B and interstitial lung abnormalities differed significantly between those with definite fibrosis and those without definite fibrosis ($P = 0.16$).

MUC5B GENOTYPE, LUNG ABNORMALITIES, AND SMOKING STATUS

Although there was no evidence that smoking status modified the association between MUC5B and interstitial lung abnormalities ($P = 0.86$), on the basis of the known associations between smoking and such abnormalities,^{1,6} we evaluated the associations between the MUC5B genotype and lung abnormalities, stratified according to smoking status. For each copy of the MUC5B variant, participants who had never smoked had more than double the odds of having lung abnormalities (odds ratio, 2.4; 95% CI, 1.4 to 4.2; $P = 0.002$); similarly, current or former smokers had more than triple the odds (odds ratio, 3.2; 95% CI, 2.0 to 4.9; $P < 0.001$).

Table 2. Association between Interstitial Lung Abnormalities and *MUC5B* Genotype in the Framingham Heart Study.*

Status of Interstitial Lung Abnormalities	No. of Patients	<i>MUC5B</i> Genotype (rs35705950)			Adjusted Odds Ratio (95% CI)†	P Value	Adjusted Odds Ratio with Covariates (95% CI)‡	P Value
		G/G	G/T	T/T				
		no. of participants (%)						
Absence of interstitial lung abnormalities	1370	1113 (81)	247 (18)	10 (<1)	1.0	1.0		
Presence of interstitial lung abnormalities	177	115 (65)	56 (32)	6 (3)	2.3 (1.6–3.1)	<0.001	2.8 (2.0–3.9)	<0.001
Definite fibrosis§	47	26 (55)	20 (43)	1 (2)	3.0 (1.8–5.0)	<0.001	6.3 (3.1–12.7)	<0.001

* All odds ratios are for the comparison with patients with no interstitial lung abnormalities.

† Odds ratios in this category have been adjusted for familial relationships with the use of multivariate logistic-regression models, as described previously.¹⁷

‡ Odds ratios in this category have been adjusted for familial relationships and additional covariates, including age, sex, body-mass index, pack-years of smoking, and current or former smoking status.

§ Definite fibrosis is defined as interstitial lung abnormalities limited to those with architectural distortion highly suggestive of a fibrotic lung disease.¹⁵

DISCUSSION

In our study, the *MUC5B* promoter polymorphism was associated with interstitial lung abnormalities, as observed on CT scans of the lung in a general population sample. We found that such abnormalities were common and occurred in nearly 9% of this population among persons over the age of 50 years. Definite fibrosis was observed in approximately 2% of the study population over the age of 50 years. Interstitial lung abnormalities are associated with reduced lung volumes and diffusion capacity, as well as increased respiratory symptoms and the presence of the *MUC5B* genotype. Although the evidence for an association between the *MUC5B* genotype and lung abnormalities was stronger among older persons, it did not appear to be influenced by cigarette smoking.

Previously, we reported that interstitial lung abnormalities were associated with reduced total lung volume¹ and reduced exercise capacity⁶ among smokers. This study extends these findings by showing that such abnormalities are also associated with increased respiratory symptoms, reduced total lung capacity, and reduced diffusion capacity of carbon monoxide in the general population. Our genetic-association study of interstitial lung abnormalities in the general population adds to studies of patients with familial interstitial pneumonia²² and shows that at least some component of the genetic predisposition for interstitial lung abnormalities and idiopathic

pulmonary fibrosis is shared. The common association between *MUC5B* genotype, idiopathic pulmonary fibrosis,⁸ and now a phenotype in the general population that includes abnormalities on imaging, physiological abnormalities, and gas-exchange abnormalities suggests that, in at least some cases, interstitial lung abnormalities may represent an early or subclinical stage of pulmonary fibrosis. Moreover, our findings suggest that the *MUC5B* promoter polymorphism could be used to identify persons at risk for this condition.

Although the *MUC5B* genotype is associated with both idiopathic pulmonary fibrosis⁸ and an imaging phenotype suggestive of subclinical pulmonary fibrosis, the difference in the prevalence of these two conditions challenges us to consider the implications of these findings. To start, it is important to draw a distinction between interstitial lung abnormalities and idiopathic pulmonary fibrosis, since the latter is usually present in symptomatic patients and is specifically defined by a combination of histopathological and imaging features suggestive of advanced pulmonary parenchymal architectural remodeling.¹⁰ In contrast, interstitial lung abnormalities, by definition, are present in persons with undiagnosed (and often asymptomatic) disease and encompass imaging features suggestive of interstitial lung disease but not limited to those suggestive of advanced pulmonary parenchymal architectural remodeling. In addition, a comparison of the reported prevalence of these

two conditions is intriguing. Idiopathic pulmonary fibrosis is reported to be present in approximately 0.002 to 0.04% of the general population,^{10,23-27} a prevalence that increases with age (e.g., ages 45 to 55 years, 0.02 to 0.04%; ≥ 75 years of age, 0.07 to 0.30%).²⁴ Although the prevalence of interstitial lung abnormalities also increases with age,¹ the estimates of the prevalences of interstitial lung abnormalities and definite fibrosis among participants in the Framingham Heart Study who were older than 50 years of age were 9% and 2%, respectively — rates that are both substantially greater than the rate reported for idiopathic pulmonary fibrosis.

Although we cannot definitively account for the reasons underlying these discrepancies within the context of our study, a number of explanations are possible. First, interstitial lung abnormalities may represent a range of histopathological conditions, with only some of these conditions representing an early stage of idiopathic pulmonary fibrosis. In light of this factor, it is important to note that idiopathic pulmonary fibrosis is reported to be the most common form of idiopathic interstitial pneumonia¹⁰ and interstitial lung disease in general.²⁷ Second, idiopathic pulmonary fibrosis may be underdiagnosed or underreported. In support of this conclusion, a study from Bernalillo County, New Mexico, noted that the prevalence of interstitial lung disease was underreported on death certificates, whereas a review of 510 autopsy reports estimated that the overall prevalence of interstitial lung disease was 1.8% and that approximately half of these cases could be attributed to idiopathic pulmonary fibrosis.²⁶ Finally, the diagnosis of idiopathic pulmonary fibrosis may come at an advanced stage of a more common, and often minimally symptomatic, pulmonary fibrosis syndrome that progresses in persons at various rates.

Our study has several limitations. First, some participants in the Framingham Heart Study with interstitial lung abnormalities could be misclassified (i.e., could have similar imaging changes because of conditions other than interstitial lung disease or pulmonary fibrosis). Although this explanation may be true for select participants, it does not explain the physiological and genetic findings we report here. We suggest that even among genetic-association studies involving rare diseases, misclassification bias could be an important factor in limit-

ing the interpretation, since controls may not have been accurately phenotyped.

Second, although we do not have definitive evidence that age modifies the association between the *MUC5B* genotype and interstitial lung abnormalities, the limited evidence of a genetic association and the reduced prevalence of such abnormalities among persons 50 years of age or younger suggest that chest CT is unlikely to be useful in genetic studies of interstitial lung abnormalities in this age group.

Third, as we discussed above, the sample size of our study may limit our ability to draw definitive conclusions, particularly from interaction analyses. In considering sample size, it is important to note that this study accounts for all participants in the Framingham Heart Study in whom volumetric thoracic chest CT was performed. In addition, our comparison groups are stratified on the basis of genetic markers and our phenotypes were prospectively obtained by readers who were unaware of any genetic or patient-specific information.

Fourth, it is important to note that the Framingham Heart Study is a general population sample of adults of predominantly European descent.¹¹ We urge caution in extrapolating our findings, particularly in relation to *MUC5B* genotype, to younger populations and those with different environmental exposures or genetic backgrounds, since in such groups, the reported prevalence of the minor allele of rs35705950 has been much lower.⁹

Finally, because of linkage-disequilibrium patterns on chromosome 11p15.5, we urge caution in interpreting the functional significance of rs35705950 until comprehensive resequencing of this genomic region has been performed and this variant can be clearly established as the causative variant.

Our study shows that interstitial lung abnormalities are present in approximately 1 in 11 persons 50 years of age or older, according to our population sample. These imaging abnormalities are linked to physiological abnormalities that are also present in patients with idiopathic pulmonary fibrosis. Moreover, the *MUC5B* promoter polymorphism appears to identify persons who are at particularly high risk for interstitial lung abnormalities and imaging evidence of pulmonary fibrosis, as was previously reported for patients with idiopathic pulmonary fibrosis or familial interstitial pneumonia.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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REFERENCES

1. Washko GR, Hunninghake GM, Fernandez IE, et al. Lung volumes and emphysema in smokers with interstitial lung abnormalities. *N Engl J Med* 2011;364:897-906.
2. Bitterman PB, Rennard SI, Keogh BA, Wewers MD, Adelberg S, Crystal RG. Familial idiopathic pulmonary fibrosis: evidence of lung inflammation in unaffected family members. *N Engl J Med* 1986;314:1343-7.
3. Steele MP, Speer MC, Loyd JE, et al. Clinical and pathologic features of familial interstitial pneumonia. *Am J Respir Crit Care Med* 2005;172:1146-52.
4. El-Chemaly S, Ziegler SG, Calado RT, et al. Natural history of pulmonary fibrosis in two subjects with the same telomerase mutation. *Chest* 2011;139:1203-9.
5. Ley B, Collard HR, King TE Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011;183:431-40.
6. Lederer DJ, Enright PL, Kawut SM, et al. Cigarette smoking is associated with subclinical parenchymal lung disease: the Multi-Ethnic Study of Atherosclerosis (MESA)-lung study. *Am J Respir Crit Care Med* 2009;180:407-14.
7. Doyle TJ, Washko GR, Fernandez IE, et al. Interstitial lung abnormalities and reduced exercise capacity. *Am J Respir Crit Care Med* 2012;185:756-62.
8. Seibold MA, Wise AL, Speer MC, et al. A common MUC5B promoter polymorphism and pulmonary fibrosis. *N Engl J Med* 2011;364:1503-12.
9. Online Mendelian Inheritance in Man. Mucin 5, subtype B, tracheobronchial: MUC5B. OMIM no. 600770 (<http://www.omim.org/entry/600770?search=600770&highlight=600770>).
10. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011;183:788-824.
11. Framingham Heart Study home page (<http://www.framinghamheartstudy.org/index.html>).
12. Ferris BG Jr, Speizer FE, Bishop Y, Prang G, Weener J. Spirometry for an epidemiologic study: deriving optimum summary statistics for each subject. *Bull Eur Physiopathol Respir* 1978;14:145-66.
13. Janson C, Anto J, Burney P, et al. The European Community Respiratory Health Survey: what are the main results so far? European Community Respiratory Health Survey II. *Eur Respir J* 2001;18:598-611.
14. Xu JF, Washko GR, Nakahira K, et al. Statins and pulmonary fibrosis: the potential role of NLRP3 inflammasome activation. *Am J Respir Crit Care Med* 2012;185:547-56.
15. Lee HY, Seo JB, Steele MP, et al. The high-resolution CT scan findings in familial interstitial pneumonia do not conform to those of idiopathic interstitial pneumonia. *Chest* 2012;142:1577-83.
16. Ross JC, Estépar RS, Díaz A, et al. Lung extraction, lobe segmentation and hierarchical region assessment for quantitative analysis on high resolution computed tomography images. *Med Image Comput Assist Interv* 2009;12:690-8.
17. Uh HW, Wijk HJ, Houwing-Duistermaat JJ. Testing for genetic association taking into account phenotypic information of relatives. *BMC Proc* 2009;3:Suppl 7:S123. abstract.
18. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179-87.
19. Miller A, Thornton JC, Warshaw R, Anderson H, Teirstein AS, Selikoff JJ. Single breath diffusing capacity in a representative sample of the population of Michigan, a large industrial state: predicted values, lower limits of normal, and frequencies of abnormality by smoking history. *Am Rev Respir Dis* 1983;127:270-7.
20. Stocks J, Quanjer PH. Reference values for residual volume, functional residual capacity and total lung capacity: ATS Workshop on Lung Volume Measurements: official statement of the European Respiratory Society. *Eur Respir J* 1995;8:492-506.
21. Hourihane DO, Lessof L, Richardson PC. Hyaline and calcified pleural plaques as an index of exposure to asbestos. *Br Med J* 1966;1:1069-74.
22. Diaz de Leon A, Cronkhite JT, Yilmaz C, et al. Subclinical lung disease, macrocytosis, and premature graying in kindreds with telomerase (TERT) mutations. *Chest* 2011;140:753-63.
23. Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2006;174:810-6.
24. Iwai K, Mori T, Yamada N, Yamaguchi M, Hosoda Y. Idiopathic pulmonary fibrosis: epidemiologic approaches to occupational exposure. *Am J Respir Crit Care Med* 1994;150:670-5.
25. Fernández Pérez ER, Daniels CE, Schroeder DR, et al. Incidence, prevalence, and clinical course of idiopathic pulmonary fibrosis: a population-based study. *Chest* 2010;137:129-37.
26. Coultas DB, Zumwalt RB, Black WC, Sobonya RE. The epidemiology of interstitial lung diseases. *Am J Respir Crit Care Med* 1994;150:967-72.
27. Gribbin J, Hubbard RB, Le Jeune I, Smith CJ, West J, Tata LJ. Incidence and mortality of idiopathic pulmonary fibrosis and sarcoidosis in the UK. *Thorax* 2006;61:980-5.

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