ORIGINAL ARTICLE

MUC5B Promoter Variant and Rheumatoid Arthritis with Interstitial Lung Disease

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ABSTRACT

BACKGROUND

Given the phenotypic similarities between rheumatoid arthritis (RA)–associated interstitial lung disease (ILD) (hereafter, RA-ILD) and idiopathic pulmonary fibrosis, we hypothesized that the strongest risk factor for the development of idiopathic pulmonary fibrosis, the gain-of-function *MUC5B* promoter variant rs35705950, would also contribute to the risk of ILD among patients with RA.

METHODS

Using a discovery population and multiple validation populations, we tested the association of the *MUC5B* promoter variant rs35705950 in 620 patients with RA-ILD, 614 patients with RA without ILD, and 5448 unaffected controls.

RESULTS

Analysis of the discovery population revealed an association of the minor allele of the *MUC5B* promoter variant with RA-ILD when patients with RA-ILD were compared with unaffected controls (adjusted odds ratio, 3.8; 95% confidence interval [CI], 2.8 to 5.2; $P=9.7\times10^{-17}$). The *MUC5B* promoter variant was also significantly overrepresented among patients with RA-ILD, as compared with unaffected controls, in an analysis of the multiethnic case series (adjusted odds ratio, 5.5; 95% CI, 4.2 to 7.3; $P=4.7\times10^{-35}$) and in a combined analysis of the discovery population and the multiethnic case series (adjusted odds ratio, 4.7; 95% CI, 3.9 to 5.8; $P=1.3\times10^{-49}$). In addition, the *MUC5B* promoter variant was associated with an increased risk of ILD among patients with RA (adjusted odds ratio in combined analysis, 3.1; 95% CI, 1.8 to 5.4; $P=7.4\times10^{-5}$), particularly among those with evidence of usual interstitial pneumonia on high-resolution computed tomography (adjusted odds ratio in combined analysis, 6.1; 95% CI, 2.9 to 13.1; $P=2.5\times10^{-6}$). However, no significant association with the *MUC5B* promoter variant was observed for the diagnosis of RA alone.

CONCLUSIONS

We found that the *MUC5B* promoter variant was associated with RA-ILD and more specifically associated with evidence of usual interstitial pneumonia on imaging. (Funded by Société Française de Rhumatologie and others.)

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Rheumatoid arthritis (RA) is a common inflammatory and autoimmune disease that is associated with progressive impairment, systemic complications, and increased mortality.[1] Interstitial lung disease (ILD) is detected in up to 60% of patients with RA on high-resolution computed tomography (CT), is clinically significant in 10% of cases, and is a leading cause of illness and death in patients with RA.[2-6]

RA-associated ILD (RA-ILD) shares several characteristics with idiopathic pulmonary fibrosis, including common environmental risk factors,[7,8] a high prevalence of a pattern of usual interstitial pneumonia (UIP),[9] progressive lung fibrosis, and poor survival.[10,11] In the French population, the prevalence of a UIP pattern is 3.4 to 12.1 times as high among patients with RA as in the general population (see the Supplementary Appendix, available with the full text of this article at NEJM .org).[5,12-14] Consequently, the occurrence of a UIP pattern in patients with RA should not be considered incidental. An exome-sequencing study showed that patients with RA-ILD had an excess of mutations in genes that were previously linked to familial interstitial pneumonia, including *TERT*, *RTEL1*, *PARN*, and *SFTPC*.[15]

The common gain-of-function variant rs35705950[16] in the promoter of *MUC5B*, encoding mucin 5B, is the strongest genetic risk factor for idiopathic pulmonary fibrosis; it is observed in at least 50% of patients with idiopathic pulmonary fibrosis and accounts for 30% of the risk of developing this disease.[17-25] This variant is associated with increased expression of *MUC5B* in lung parenchyma of unaffected controls and of persons with idiopathic pulmonary fibrosis.[16,17] Consequently, we hypothesized that the *MUC5B* promoter variant would also be associated with an increased risk of RA-ILD. To test this hypothesis, we tested the association of the *MUC5B* promoter variant with RA-ILD in eight case series in seven countries.

Methods

Study Populations

The discovery population included patients with RA, with or without ILD as assessed by high-resolution CT of the chest, and unaffected persons, all from the French RA-ILD network.[15] The multiethnic replication case series were obtained from six countries (one case series each from China, Greece, Japan, Mexico, and the Netherlands and two from the United States [designated United States–1 and United States–2]). All cases fulfilled the 2010 European League against Rheumatism–American College of Rheumatology criteria or 1987 American College of Rheumatology revised criteria for RA.[26,27] The ILD status of patients with RA was established by chest high-resolution CT images that were centrally reviewed by experienced readers. However, in the United States–1 case series, the absence of ILD (i.e., phenotype of RA without ILD) was determined by patient report. The chest high-resolution CT pattern was classified as UIP, possible UIP, or inconsistent with UIP, according to international criteria.[28] The institutional review board at each institution approved all protocols, and all patients provided written informed consent.

Genotyping

Genotyping of the *MUC5B* rs35705950 single-nucleotide polymorphism involved the use of TaqMan Genotyping Assays (Applied Biosystems), as reported previously.[17] The additional common risk variants for idiopathic pulmonary fibrosis on 3q26, 4q22, 5p15, 6p21.3, 6p24, 7q22, 10q24, 11p15.5, 13q34, 15q14–15, and 19p13[19,20,29] were genotyped by a TaqMan quantitative polymerase-chain-reaction assay (Thermo Fisher Scientific).

Lung-Tissue Analysis

To determine whether MUC5B was expressed in the lung tissue of patients with RA-ILD, we analyzed lung tissue from nine patients with RA-ILD undergoing lung transplantation (University of California, San Francisco) as compared with six unaffected controls without ILD or RA (National Heart, Lung, and Blood Institute [NHLBI] Lung Tissue Research Consortium) and two controls with fibrotic ILD without RA (both with desquamative interstitial pneumonia) (NHLBI Lung Tissue Research Consortium).

Statistical Analysis

Association analyses were performed with the use of logistic regression with no covariate (results are reported as crude) and with adjustment for sex, age at inclusion, smoking status (ever smoked vs. never smoked), country of origin, or a combination of these. For each *MUC5B* promoter variant association test, the best-fitting model (dominant or additive) was considered with the use of the Akaike information criterion. Interaction between the vari-

ant and smoking status was tested according to the significance of the interaction term in logistic regression. The effect of RA-ILD with a UIP or possible UIP pattern as compared with RA without ILD and of RA-ILD with a pattern inconsistent with UIP as compared with RA without ILD was assessed with the use of a z-test on the effect sizes of the logistic regression. A P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

STUDY POPULATIONS

The discovery population included 118 patients with RA-ILD, 105 patients with RA without ILD, and 1229 unaffected controls. The multiethnic replication sample included 502 patients with RA-ILD, 509 patients with RA without ILD, and 4219 unaffected controls (Table S1 in the Supplementary Appendix).

CHARACTERISTICS OF THE DISCOVERY POPULATION

As compared with patients with RA without ILD, those with RA-ILD were more likely to be male, were older, and were more likely to have ever smoked (54.7% vs. 36.1%) (Table 1). After adjustment for sex, patients with RA-ILD and those with RA without ILD did not differ significantly with respect to positivity for rheumatoid factor or anti–citrullinated protein antibody (yes or no), erosive status of RA (erosions present or not), exposure to methotrexate (yes or no), or the mean duration of RA from diagnosis to study inclusion. Overall, 41.0% of patients with RA-ILD had a UIP or possible UIP pattern on high-resolution CT.

MUC5B PROMOTER VARIANT AND RISK OF RA-ILD

Comparison of patients with RA without ILD and controls revealed that none of the case series (discovery population and multiethnic case series) showed a significant difference in the frequency of the *MUC5B* promoter variant (Table 2 and Fig. 1A), findings that suggest a lack of association between the *MUC5B* promoter variant and RA. In the discovery population, the minor allele frequency of the *MUC5B* promoter variant was 10.9% in unaffected controls and 32.6% in patients with RA-ILD; this variant was in Hardy–Weinberg equilibrium in the discovery population. After controlling for sex, we detected a significant association between the *MUC5B* promoter variant and RA-ILD when we compared patients with RA-ILD and unaffected controls (adjusted odds ratio, 3.8; 95% confidence interval [CI], 2.8 to 5.2; $P=9.7\times10^{-17}$) (Table 2).

The *MUC5B* promoter variant was significantly overrepresented among patients with RA-ILD, as compared with unaffected controls, in each of the multiethnic case series, except in the two Asian case series (Table 2). The *MUC5B* promoter variant is underrepresented in Asian populations; consequently, the tests for association in the two case series of Asian persons were underpowered and we did not observe a significant relationship between the *MUC5B* promoter variant and RA-ILD in these two case series.

An analysis of the multiethnic case series showed a significant association between the *MUC5B* promoter variant and RA-ILD (adjusted odds ratio, 5.5; 95% CI, 4.2 to 7.3; $P=4.7\times10^{-35}$) (Table 2 and Fig. 1B), and an analysis of all the series (discovery population together with the other case series) combined showed a similar significant association for this comparison (adjusted odds ratio, 4.7; 95% CI, 3.9 to 5.8; $P=1.3\times10^{-49}$). For the comparison with unaffected controls, the best-fitting genetic model for the three study populations (discovery population, aggregate multiethnic case series, and combined analysis) for the association of the *MUC5B* promoter variant and RA-ILD was dominant (Tables S4 through S6 in the Supplementary Appendix).

MUC5B PROMOTER VARIANT AND RISK OF ILD AMONG PATIENTS WITH RA

To investigate whether the *MUC5B* promoter variant rs35705950 contributes to the risk of ILD among patients with RA, we compared patients with RA-ILD and those with RA without ILD, adjusting for sex, age at inclusion, and smoking status. In the discovery population, the *MUC5B* promoter variant was associated with RA-ILD (adjusted odds ratio, 3.1; 95% CI, 1.6 to 6.3; $P=9.4\times10^{-4}$), and this finding was replicated in the aggregate multiethnic case series (adjusted odds ratio, 2.9; 95% CI, 1.1 to 8.4; $P=0.04$) as well as the combined analysis (adjusted odds ratio, 3.1; 95% CI, 1.8 to 5.4; $P=7.4\times10^{-5}$) (Table 2 and Fig. 1C). For the comparison of RA-ILD with RA without ILD, the best-fitting genetic model for the three study populations (discovery population, aggregate multiethnic case series, and combined analysis) was dominant (Table S6 in the Supple-

Table 1. Baseline Characteristics of Patients with Rheumatoid Arthritis (RA).*

Characteristic	RA-ILD (N=620)	RA without ILD (N=614)	Crude P Value	Adjusted P Value†
Female sex — no./total no. (%)	345/565 (61.1)	446/540 (82.6)	8.12×10^{-15}	3.7×10^{-12}‡
Age at inclusion — yr	69.0±10.8	60.4±12.6	1.20×10^{-24}	1.3×10^{-21}
Age at onset of RA — yr	55.7±14.6	45.7±13.5	7.0×10^{-23}	5.6×10^{-14}
Duration of RA — yr	13.3±11.5	14.8±10.2	0.03	0.38
Age at onset of ILD — yr	62.7±11.8			
Duration of ILD — yr	4.3±4.0			
Ever smoked				
No./total no. (%)	282/516 (54.7)	168/465 (36.1)	7.59×10^{-9}	0.53
Pack-yr of smoking	28.0±21.8	22.4±30.7	0.07	0.37
Current smoker				
No./total no. (%)	46/415 (11.1)	67/463 (14.5)	0.14	0.06
Pack-yr of smoking	33.0±26.6	23.9±19.7	0.08	0.42
Ever used methotrexate — no./total no. (%)§	260/318 (81.8)	142/153 (92.8)	0.002	0.69
Manifestations of RA				
Positivity for ACPA or rheumatoid factor — no./total no. (%)	449/506 (88.7)	446/468 (95.3)	0.001	0.72
Erosive disease — no./total no. (%)	224/482 (46.5)	274/469 (58.4)	2.33×10^{-4}	0.30
Disease pattern on high-resolution CT of the chest				
UIP or possible UIP — no./total no. (%)	207/505 (41.0)			
Inconsistent with UIP — no./total no. (%)	298/505 (59.0)			
Pulmonary function				
Forced vital capacity — % of predicted value	78.2±25.0			
DLco — % of predicted value	57.6±23.4			
Total lung capacity — % of predicted value	81.3±20.3			

* Plus–minus values are means ±SD. ACPA denotes anti–citrullinated protein antibody, CT computed tomography, DLco diffusing capacity of the lung for carbon monoxide, ILD interstitial lung disease, RA-ILD rheumatoid arthritis–associated interstitial lung disease, and UIP usual interstitial pneumonia.
† P values were adjusted for sex and country of origin, except where indicated.
‡ The P value was adjusted for country of origin only.
§ To avoid any prescription bias resulting from the co-occurrence of ILD, the methotrexate exposure was established during the period before the diagnosis of ILD.

mentary Appendix). After adjustment for covariates, no association between smoking status and risk of ILD among patients with RA was found (adjusted odds ratio, 0.7; 95% CI, 0.3 to 1.9; P=0.51) and no interaction of tobacco-smoke exposure with the *MUC5B* promoter variant was observed (Table S7 in the Supplementary Appendix).

MUC5B PROMOTER VARIANT AND UIP PATTERN

When we limited patients with RA-ILD to those with evidence (by high-resolution CT scan) of a UIP or possible UIP pattern, we observed an association between the *MUC5B* promoter variant and a UIP or possible UIP pattern in the discovery population (adjusted odds ratio, 5.0; 95% CI, 2.1 to 12.3; $P=3.0\times10^{-4}$), in the aggregate multiethnic case series (adjusted odds ratio, 9.2; 95% CI, 2.3 to 38.7; P=0.002), and in the combined case series analysis (adjusted odds ratio, 6.1; 95% CI, 2.9 to 13.1; $P=2.5\times10^{-6}$) (Fig. 1C, and Table S2 in the Supplementary Appendix). In the combined analysis, the comparison of odds ratios for RA-ILD with a UIP or possible UIP pattern versus RA without ILD (adjusted odds ratio, 6.1 [noted previously]) and RA-ILD with a pattern inconsistent with UIP versus RA without ILD (adjusted odds ratio,

Table 2. Genotypic Association of *MUC5B* rs35705950 Single-Nucleotide Polymorphism in Patients with RA, with and without ILD, and Unaffected Controls.*

Variable	France†	Greece	The Netherlands	United States–1	United States–2	Mexico	Japan	China	Multiethnic Replication Sample	Combined Analysis
No. of persons										
Controls	1229	1795	249	500	—	347	315	1013	4219	5448
RA without ILD	105	—	—	68	72	69	300	—	509	614
RA-ILD	118	56	40	99	48	55	182	22	502	620
Minor allele frequency of *MUC5B* rs35705950 — %										
Controls	10.9	3.8	9.0	10.7	—	5.3	0.2	0.8	—	—
RA without ILD	12.9	—	—	11.0	12.5	3.6	0.5	—	—	—
RA-ILD	32.6	26.8	30.0	28.8	13.5	16.4	1.1	2.3	—	—
Genotypic association test										
RA without ILD vs. controls										
Crude odds ratio for RA without ILD (95% CI)	1.2 (0.8–1.8)	—	—	1.0 (0.6–1.8)	—	0.7 (0.2–1.6)	3.2 (0.4–64.3)	—	1.0 (0.6–1.5)	1.1 (0.8–1.5)
Crude P value	0.40	—	—	0.91	—	0.42	0.32	—	0.90	0.60
Adjusted odds ratio for RA without ILD (95% CI)‡	1.3 (0.8–1.9)	—	—	1.0 (0.5–1.7)	—	0.7 (0.2–1.7)	3.7 (0.5–75.1)	—	1.0 (0.6–1.5)	1.1 (0.8–1.5)
Adjusted P value‡	0.28	—	—	0.99	—	0.42	0.26	—	0.83	0.54
RA-ILD vs. controls										
Crude odds ratio for RA-ILD (95% CI)	3.8 (2.8–5.2)	13.2 (7.6–22.9)	5.6 (2.9–11.2)	4.1 (2.7–6.3)	—	3.4 (1.8–6.2)	7.1 (1.0–138.6)	3.0 (0.2–15.6)	5.5 (4.2–7.2)	4.7 (3.8–5.8)
Crude P value	3.8×10^{-17}	2.2×10^{-20}	5.0×10^{-7}	5.8×10^{-11}	—	1.1×10^{-4}	0.08	0.30	3.9×10^{-35}	1.3×10^{-49}
Adjusted odds ratio for RA-ILD (95% CI)‡	3.8 (2.8–5.2)	13.2 (7.6–23.0)	4.9 (2.2–11.5)	4.1 (2.7–6.3)	—	3.6 (1.8–7.3)	5.5 (0.6–119.1)	4.9 (0.3–27.5)	5.5 (4.2–7.3)	4.7 (3.9–5.8)
Adjusted P value‡	9.7×10^{-17}	6.2×10^{-20}	1.2×10^{-4}	5.6×10^{-11}	—	2.2×10^{-4}	0.16	0.14	4.7×10^{-35}	1.3×10^{-49}
RA-ILD vs. RA without ILD										
Crude odds ratio for RA-ILD (95% CI)	3.8 (2.2–6.8)	—	—	5.4 (2.6–11.7)	1.1 (0.5–2.5)	5.7 (2.1–18.6)	2.2 (0.5–11.4)	—	3.1 (2.0–5.0)	3.4 (2.4–4.8)
Crude P value	5.9×10^{-6}	—	—	7.9×10^{-6}	0.80	0.002	0.30	—	5.3×10^{-7}	1.6×10^{-11}
Adjusted odds ratio for RA-ILD (95% CI)§	3.1 (1.6–6.3)	—	—	NA	NA	3.8 (1.2–13.3)	3.1 (0.3–28.0)	—	2.9 (1.1–8.4)	3.1 (1.8–5.4)
Adjusted P value§	9.4×10^{-4}	—	—	NA	NA	0.03	0.30	—	0.04	7.4×10^{-5}

* The two case series from the United States are designated United States–1 and United States–2. CI denotes confidence interval, and RA-ILD rheumatoid arthritis–associated interstitial lung disease.
† The case series from France represents the discovery population.
‡ P values and odds ratios were adjusted for sex and country of origin.
§ P values and odds ratios were adjusted for sex, age at inclusion, smoking status (ever smoked vs. never smoked), and country of origin. Some odds ratios and P values are not available (NA) because not all covariates were available for adjustment.

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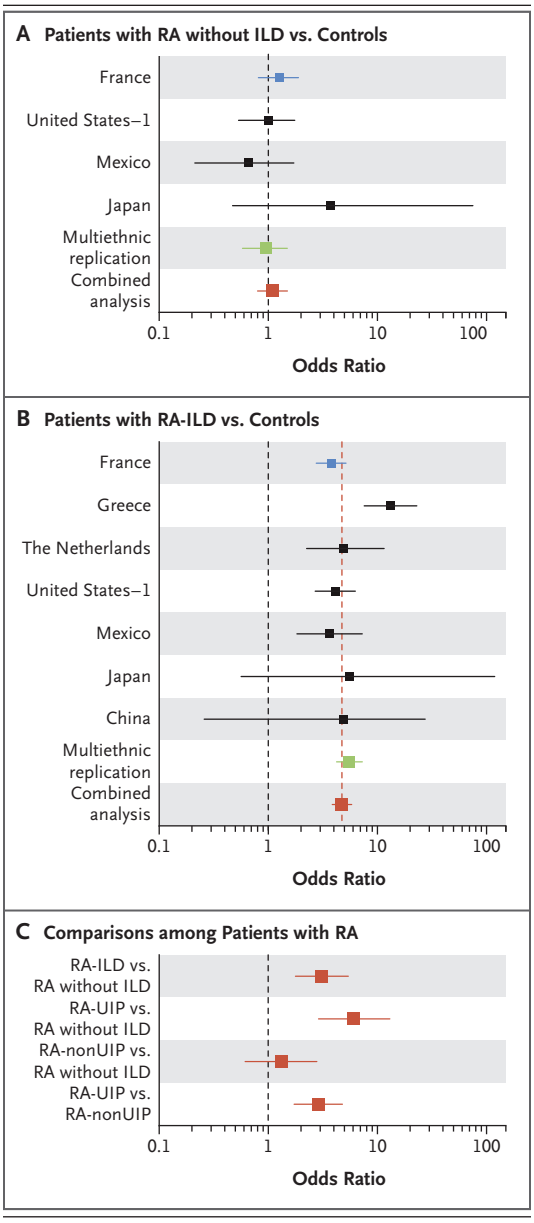

Figure 1. Association of the *MUC5B* rs35705950 Promoter Variant with Rheumatoid Arthritis (RA)–Associated Interstitial Lung Disease (ILD) (RA-ILD).

Shown are forest plots of odds ratios and 95% confidence intervals. The boxes indicate odds ratios, and the horizontal lines indicate 95% confidence intervals for the best-fitting genetic model (dominant or additive) for each association test. The black dashed line represents a mean odds ratio value of 1. The red boxes and red lines indicate the overall odds ratios and 95% confidence intervals, respectively. The case series from France represents the discovery population. For comparisons between patients with RA and controls, the associations were adjusted for the country of origin and sex. For comparisons among patients with RA, the associations were adjusted for the country of origin, sex, age at inclusion, and smoking status. Panel A shows a lack of association of the *MUC5B* promoter variant rs35705950 with RA without ILD. Panel B shows an additive genotypic association of the *MUC5B* promoter variant rs35705950 with RA-ILD. The red dashed line represents the mean overall odds ratio value. In Panels A and B, United States–1 indicates one of two case series from the United States. Panel C shows a dominant genotypic association of the *MUC5B* promoter variant rs35705950 with ILD among patients with RA and those with a pattern of usual interstitial pneumonia (UIP) or possible UIP. RA-UIP denotes RA-ILD and a UIP or possible UIP pattern, and RA-nonUIP denotes RA-ILD and a pattern inconsistent with UIP.

1.3; 95% CI, 0.6 to 2.8; P=0.46) was significant (P=0.02), a finding that suggests that the effect of the *MUC5B* promoter variant was restricted to the subphenotype of RA-ILD with a UIP or possible UIP pattern (Fig. 1C, and Tables S2 and S3 in the Supplementary Appendix).

The *MUC5B* promoter variant was associated with an increased risk of a UIP pattern among patients with RA-ILD through a dominant model in the discovery population, aggregate multiethnic case series, and combined analysis; the odds of having a UIP or possible UIP pattern among patients with RA-ILD who carried at least one *MUC5B* risk allele were 2.9 times as high as those among persons who had the GG genotype (adjusted odds ratio, 2.9; 95% CI, 1.7 to 4.8; $P=5.1\times10^{-5}$) (Table 3 and Fig. 1C, and Fig. S1 in the Supplementary Appendix). After adjusting for covariates, we observed no effect of tobacco smoking on the association of the *MUC5B* promoter variant and UIP pattern of RA-ILD (Table S7 in the Supplementary Appendix).

SITES OF MUC5B EXPRESSION IN RA-ILD

Similar to observations of MUC5B expression in the lungs of persons with idiopathic pulmonary fibrosis,[17] staining of the lung tissue of patients with RA-ILD showed MUC5B in the cytoplasm of bronchioles and in areas of microscopic honeycombing, including in the metaplastic epithelia lining the honeycomb cysts and mucus within cysts, which presumably produce mucus containing MUC5B (Fig. 2, and Fig. S2 in the Supplementary Appendix). MUC5B expression was limited to mucus and the epithelium in the bronchioles in unaffected controls and in patients with des-

Table 3. Dominant Genotypic Association of *MUC5B* rs35705950 Single-Nucleotide Polymorphism in Patients with RA-ILD and a Pattern of Usual Interstitial Pneumonia (UIP) or Possible UIP and in Patients with RA-ILD and a Pattern Inconsistent with UIP.*

Variable	France†	Greece	The Netherlands	United States–1	Mexico	Japan	China	Multiethnic Replication Sample	Combined Analysis
No. of patients									
RA-ILD with UIP or possible UIP pattern	50	18	18	34	19	60	8	157	207
RA-ILD with pattern inconsistent with UIP	31	38	22	42	36	122	7	267	298
Minor allele frequency of *MUC5B* rs35705950 — %									
RA-ILD with UIP or possible UIP pattern	34.0	36.1	33.3	33.8	28.9	1.7	0	—	—
RA-ILD with pattern inconsistent with UIP	12.9	21.1	25.0	23.8	8.3	0.8	7.1	—	—
Genotypic association test									
Crude odds ratio for RA-ILD with UIP or possible UIP pattern (95% CI)	6.1 (2.3–17.5)	3.6 (1.1–13.1)	2.0 (0.6–7.6)	2.3 (0.9–6.0)	6.9 (2.0–26.0)	2.1 (0.2–17.6)	NA‡	2.9 (1.7–5.0)	3.5 (2.2–5.6)
Crude P value	3.9×10^{-4}	0.04	0.29	0.08	0.003	0.47	1.0	1.5×10^{-4}	3.6×10^{-7}
Adjusted odds ratio for RA-ILD with UIP or possible UIP pattern (95% CI)§	4.9 (1.8–14.6)	2.9 (0.8–12.1)	1.6 (0.4–6.7)	2.1 (0.7–6.3)	3.8 (0.9–16.8)	NA‡	NA‡	2.3 (1.3–4.1)	2.9 (1.7–4.8)
Adjusted P value§	0.003	0.12	0.51	0.18	0.07	0.99	1.0	0.006	5.1×10^{-5}

* Patients with RA-ILD and a pattern inconsistent with UIP had the following patterns on high-resolution computed tomography: nonspecific interstitial pneumonia, organizing pneumonia, or unclassifiable ILD.
† The case series from France represents the discovery population.
‡ Odds ratios are not available (NA) because of the small proportion of carriers with risk genotypes.
§ P values and odds ratios were adjusted for sex, age at inclusion, smoking status (ever smoked vs. never smoked), and country of origin.

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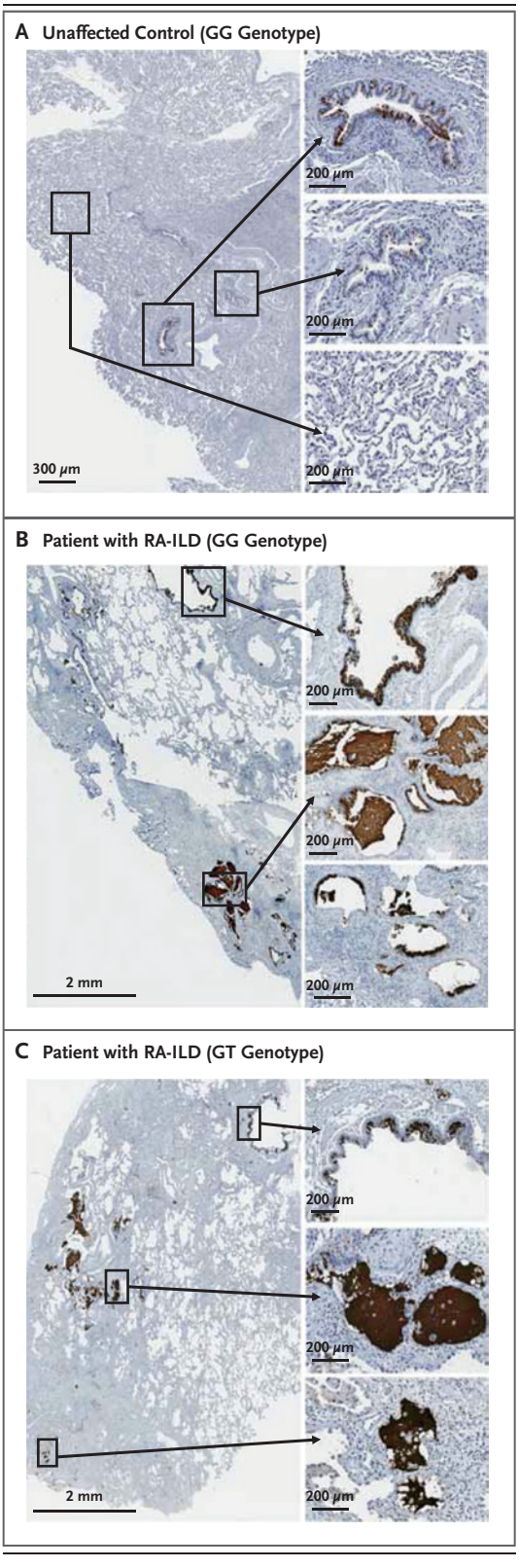

Figure 2. MUC5B Expression in Explanted Lung Tissue from Patients with RA-ILD and an Unaffected Control.

Shown are representative lung-tissue images from an unaffected control with a GG genotype (Panel A), a patient with RA-ILD and a GG genotype (Panel B), and a patient with RA-ILD and a GT genotype (Panel C). Panel A includes a low-power view (left) of normal lung, top and middle insets with a high-power view of bronchiole with MUC5B staining, and a bottom inset with a high-power view of alveolar epithelia. Panels B and C each include a low-power view (left) of the UIP pattern in explanted lung tissue, a top inset with a high-power view of bronchiole with MUC5B staining, and middle and bottom insets with a high-power view of MUC5B staining in metaplastic epithelia lining honeycomb cysts and MUC5B staining of mucus in honeycomb cysts.

quamative interstitial pneumonia (Fig. S2 in the Supplementary Appendix). In this small sample, there were no obvious differences in MUC5B expression according to genotype.

RA-ILD and Other Risk Variants for Idiopathic Pulmonary Fibrosis

Having provided evidence for the contribution of the dominant genetic risk variant for idiopathic pulmonary fibrosis to RA-ILD, we decided to test the association of RA-ILD with 12 additional common risk variants for idiopathic pulmonary fibrosis (Table S8 in the Supplementary Appendix).[19,20,29] This exploratory study included 272 patients with RA-ILD and 242 with RA without ILD from the France and Mexico case series and the first case series in the United States. In light of the relatively small sample and low power of detection (Table S8 in the Supplementary Appendix), corresponding P values, odds ratios, and 95% confidence intervals for the 12 candidate variants were considered to be descriptive and Bonferroni correction was therefore not applied (Table S9 in the Supplementary Appendix). In the comparison between patients with RA-ILD and those with RA without ILD, 2 common risk variants for idiopathic pulmonary fibrosis — *TOLLIP* rs5743890 and *IVD* rs2034650 — showed some evidence of association with RA-ILD, and the directionality of these relationships was consistent with that observed in persons with idiopathic pulmonary fibrosis.[19,20]

DISCUSSION

We found that the *MUC5B* promoter variant rs35705950, the strongest genetic risk factor for idiopathic pulmonary fibrosis, was also a strong risk factor for RA-ILD, especially among patients with evidence of a UIP pattern on imaging. The effect of the *MUC5B* promoter variant on the development of ILD in patients with RA was similar in magnitude and direction to that observed in patients with idiopathic pulmonary fibrosis.[17,30] However, the *MUC5B* promoter variant does not appear to be a risk factor for the development of RA, a finding supported by previous genomewide association studies involving patients with RA.[31] In aggregate, our results suggest that RA consists of genetic subphenotypes and that the *MUC5B* promoter variant is associated with an increased risk of RA-ILD.

The relationship between the *MUC5B* promoter variant and RA-ILD appears to be specific to the UIP pattern and not generalizable to other autoimmune conditions of the lung. The *MUC5B* promoter variant has not been found to be associated with a risk of ILDs associated with systemic sclerosis or autoimmune myositis.[21,24,32] Unlike these other types of ILD, RA-ILD shares characteristics with idiopathic pulmonary fibrosis. These include an increased prevalence of the UIP pattern (radiologic and histologic); an increased prevalence of male sex and older age[33]; rare variants in *TERT*, *RTEL1*, *PARN*, and *SFTPC*[15]; and now the *MUC5B* promoter variant rs35705950. In aggregate, these findings suggest shared pathogenic pathways between RA-ILD and idiopathic pulmonary fibrosis.[34]

Moreover, the *MUC5B* promoter variant may prove to be a generalized risk factor for UIP disease and not simply limited to idiopathic pulmonary fibrosis and RA-ILD. In fact, emerging studies have identified the *MUC5B* promoter variant as a risk factor for chronic hypersensitivity pneumonitis,[35] another condition known to have a subphenotype of a UIP pattern. Because the presence of ILD and the UIP pattern of fibrosis is underestimated on high-resolution CT scans, our point estimates for an association with the *MUC5B* promoter variant are probably conservative.[36] As has been proposed for idiopathic pulmonary fibrosis,[37] the *MUC5B* promoter variant could be used to identify early forms of RA-ILD.

The results of our exploratory study suggest a possible contribution of both *TOLLIP* rs5743890 and *IVD* rs2034650 to RA-ILD; the associations with RA-ILD were of the same direction and magnitude to those reported in idiopathic pulmonary fibrosis.[19,20] However, these findings are tentative and require further tests of replication in independent sets of patients and controls.

Our work on understanding the genetic architecture of RA-ILD has resulted in several observations. First, RA-ILD is a complex genetic phenotype, with the minor allele of the *MUC5B* promoter variant rs35705950 identified as a risk factor for the disease. The point estimates for the association of the *MUC5B* promoter variant with RA-ILD are equivalent to those observed with idiopathic pulmonary fibrosis[17] and are substantively higher than those for the most common other risk factors for RA-ILD, including cigarette smoking[7,38,39] and the human leukocyte antigen locus for RA.[31,40] Second, our findings, together with those of others,[18,20-25,35] suggest that the *MUC5B* promoter variant is a risk factor for the UIP pattern in general. Third, our findings suggest that the *MUC5B* promoter variant could be used to detect preclinical ILD in patients with RA. Fourth, non-*MUC5B* risk variants for idiopathic pulmonary fibrosis might also contribute to the genetic background of RA-ILD. Given the shared genetic background between idiopathic pulmonary fibrosis and RA-ILD in general and RA-ILD with a UIP or possible UIP pattern in particular, we would propose that drugs that are known to be effective in treating patients with idiopathic pulmonary fibrosis be evaluated in the treatment of RA-ILD.[41,42]

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APPENDIX

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