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The *MUC5B* Promoter Variant does not Predict Progression of Interstitial Lung Disease in Systemic Sclerosis

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Abstract

Objective: To investigate the prevalence of the *MUC5B* promoter variant rs35705950 in patients with systemic sclerosis-interstitial lung disease (SSc-ILD) and whether its presence predicts response to immunosuppression with cyclophosphamide (CYC) and mycophenolate (MMF).

Methods: SSc-ILD patients who participated in Scleroderma Lung Study (SLS) II (MMF versus CYC) were included in this study (N=142). TaqMan Genotyping Assays were used to determine the *MUC5B* rs35705950 single nucleotide polymorphism. Joint models were created to examine how the presence of this variant affected the course of the forced vital capacity (FVC) over 2 years. Linear regression models were used to investigate the relationship between the presence of this variant and the change in quantitative radiographic fibrosis.

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Results: Among 128 participants who were tested for this variant, 18% possessed at least one copy of the *MUC5B* minor allele. Patients with at least one copy of this allele were similar to those without the allele with respect to age, sex, SSc subtype, ILD disease severity; however, this variant was rare among African Americans (3.7%). The presence of the MUC5B variant did not affect the course of the FVC, nor the change in quantitative radiographic fibrosis, ground glass or ILD scores in either treatment arm.

Conclusion: In the context of a randomized controlled trial for SSc-ILD, the presence of the *MUC5B* variant did not predict disease severity, nor affect treatment response to MMF or CYC. Future studies are needed to determine whether this variant affects ILD progression in other SSc cohorts and in patients receiving anti-fibrotic therapy.

Keywords

Systemic sclerosis; Interstitial lung disease; Mycophenolate mofetil; Cyclophosphamide; Biomarkers; Genetics; Polymorphism

INTRODUCTION

Although the majority of patients with systemic sclerosis (SSc) have interstitial lung disease (ILD) [1], the rate of progression of ILD varies immensely among patients. While some SSc patients experience rapid progression of ILD, other patients have stable or even improved lung function over time, both with and without ILD-targeted therapy [2]. The reason for this disparity is presently unknown.

Genetic factors may contribute to the heterogeneity that exists in the progression of ILD in patients with SSc. A common gain-of-function variant rs3570595016 in the promoter of *MUC5B* is strongly associated with idiopathic pulmonary fibrosis (IPF) [3]. MUC5B encodes Mucin 5 subtype B. Patients with IPF were found to have increased expression of MUC5B in the lungs compared with controls, and the expression of MUC5B has been linked to disordered mucosal host defense and alveolar repair, as well as damage to the bronchoalveolar unit [3]. Furthermore, the *MUC5B* promoter polymorphism is associated with improved survival in IPF [4], suggesting that this variant may play a role in defining clinical phenotypes in ILDs.

In addition to IPF, this single nucleotide polymorphism in the promoter region of *MUC5B* has been associated with ILD in the setting of rheumatoid arthritis [RA] [5]. Similar to IPF, the predominant histological pattern of fibrosis in RA is usual interstitial pneumonia (UIP). In a study of 1,234 patients with RA, half of whom had ILD, Juge and colleagues [5] demonstrated that the presence of this variant increased the odds of having ILD 3-fold. In addition, the odds of having ILD were even higher in patients with evidence of an UIP pattern on high resolution computed tomography (HRCT) [5].

In SSc, it is plausible that MUC5B may play a pathogenic role given that we and others have demonstrated that membrane tethered mucin MUC1 (also known as KL-6) is a marker of disease severity in SSc-ILD and predicts progression of ILD [6]. However, MUC1 is a distinct mucin compared with MUC5B, and prior observational studies in SSc have failed to

demonstrate a relationship between the *MUC5B* variant and the presence of ILD in SSc [7-9].

To our knowledge, no studies have evaluated the role of *MUC5B* polymorphisms in the progression of SSc-ILD in the context of a randomized controlled trial (RCT), in which all patients receive standard treatment and follow up during the trial. The goal of the present study was to evaluate whether the presence of the MUC5B rs35705950 polymorphism could: (1) discriminate between SSc patients with severe versus less severe ILD; and (2) identify patients with SSc-ILD who are more likely to experience progression of ILD, despite therapy with mycophenolate mofetil (MMF) or cyclophosphamide (CYC).

MATERIALS AND METHODS

Study participants

Participants of SLS II were included in this study [10], Eligibility criteria for SLS II included the following key inclusion criteria: (1) adults, aged 18–75 years, (2) limited or diffuse cutaneous SSc, (3) active ILD as demonstrated by restrictive to borderline restrictive ventilatory impairment (FVC<80–85%, but ≥ 45% predicted) AND the presence of any ground glass opacity (GGO; hazy opacity through which normal lung markings can be discerned) on high-resolution computed tomography (HRCT), (4) exertional dyspnea (Grade ≥2 on the Magnitude of Task component of the Mahler Baseline Dyspnea Index [BDI], Key exclusion criteria included clinically significant pulmonary hypertension, abnormalities on HRCT not attributable to SSc, and smoking within the prior 6 months to enrollment. Complete details of the SLS II study design have been previously reported [10]

The protocol was approved by a Data and Safety Monitoring Board (DSMB) constituted by the National Heart, Lung and Blood Institute, National Institutes of Health (NIH/NHLBI). The institutional review board (IRB) at the main coordinating center, University of California, Los Angeles, approved this study (11–002659-CR-00005). In addition, each of the participating centers (N=14) had IRB approval to conduct this study. All participants gave written informed consent to participate in the study and publish its findings.

SLS II Study Design

SLS II study participants were randomized in 1:1 ratio to either oral CYC for one year followed by one year of placebo or MMF for 2 years [10], The FVC was measured every 3 months during the 2 year study. HRCT thoracic imaging was obtained at baseline and 24 months, and a Computer Aided Design (CAD) scoring system calculated the quantitative extent of different patterns of ILD [11], Quantitative ILD (QILD) score was the sum of all abnormally classified scores, including scores for quantitative lung fibrosis (QLF, linear reticular markings with architectural distortion), GGO and honeycomb changes (clustered air-filled cysts with dense walls). Scores were calculated as percentage of total counted voxels for both the whole lung (WL), including both lungs, and for the zone (area-equivalent upper, middle or lower lung zone) of maximal involvement (ZM).

MUC5B Genotyping

Blood samples were collected in EDTA tubes and centrifuged. Buffy coats were separated and stored locally. Subsequently, samples were shipped on dry ice to the central biorepository at the University of Texas Health Science Center at Houston. Out of 142 SLS II participants, 129 patients had DNA samples of sufficient quantity for MUC5B rs3 5705950 genotyping. Genotyping was performed successfully in 128 out of 129 available samples (99.2%) using TaqMan Genotyping Assays.

Statistical Analysis

Summary statistics were generated for baseline characteristics. A two-sample t-test or Wilcoxon rank-sum test was used to compare continuous variables and a chi-square test or Fisher's exact test was used to compare categorical variables.

A joint model analysis was used to determine whether the presence of the *MUC5B* rs35705950 minor allele predicts progression of SSc-ILD in each treatment arm. The joint model (used also in the main SLS Π analysis [10]) adjusts for non-ignorable missing data due to treatment failure, death, and drop-outs [12]. The endpoint for the primary outcome model was the course of FVC %-predicted measured every 3 months over 24 months. The longitudinal model of the joint analysis included the following covariates: presence of at least one copy of the MUC5B minor allele (Y/N), baseline FVC %-predicted, African American race (Y/N). The trajectory of FVC was modeled using linear splines with knots at 12 and 21 months.

Linear regression models were created to examine whether the presence of the *MUC5B* minor allele affected the change in the QLF-ZM/WL, QILD-ZM/WL, QGGO-ZM/WL. Covariates for the linear regression analyses included: presence of at least one copy of the MUC5B minor allele (Y/N), baseline QLF/QILD score, African American race (Y/N), and treatment arm.

All tests were 2-sided. The joint analyses were performed using the R package JMbayes, and all other analyses were conducted in SAS v9.4 (The SAS Institute, Cary, NC).

RESULTS

Participant Characteristics

Of the 142 participants of SLS II, 128 underwent *MUC5B* genotyping analysis. The genotype count for the GG, GT, and TT variants were 105, 20, 3, resulting in a minor allele frequency of 10.2%. Following the dominance inheritance mode, 23 (18%) patients had at least one copy of *MUC5B* rs35705950 minor allele. The MUC5B genotyping results did not significantly deviate from Hardy-Weinberg equilibrium (p=0.126).

There were no significant differences in baseline demographic characteristics between patients with and without the *MUC5B* rs35705950 minor allele (Table 1), with the exception of race. In this study, only 3.7% (N=1) of African American participants had at least one copy of MUC5B minor allele. There were also significant differences in SSc diseases features (SSc subtype [diffuse vs. limited], disease duration, modified Rodnan skin score

[mRSS]), or ILD disease severity (degree of restriction, extent of radiographic fibrosis and ILD) between patients with and without this allele (Table 1).

MUC5B and the Course of the FVC

The presence of the *MUC5B* minor allele did not predict the course of the FVC%-predicted from 3 to 24 months in either treatment arm (Figure 1). Specifically, there were no significant interactions between the presence of this allele and any of the time trends (3-12 months, 12-21 months, 21-24 months) in the joint model analyses for the CYC (Table 2) or MMF (Table 3) arms. In both joint model analyses (CYC and MMF arms), baseline FVC%-predicted was the strongest predictor of the course of the FVC%-predicted from 3 to 24 months. Specifically, patients in both treatment arms with a higher FVC%-predicted at baseline had an improved course of the FVC%-predicted over the course of the study..

MUC5B and Changes in Radiographic Fibrosis

The linear regression analyses demonstrated that the presence of the *MUC5B* minor allele was not significantly associated with changes in the quantitative extent of lung fibrosis, GGO or ILD in SLS II participants. Even after adjusting for treatment arm and baseline radiographic fibrosis scores, the presence of this gene variant was not associated with a change in the QLF (ZM), QILD (ZM and WL), QGGO (ZM and WL) scores from baseline to 24 months (Table 4). There was a trend that the presence of the *MUC5B* minor allele was associated with worsening QLF in the WL ($P = 0.073$). Given the paucity of patients who demonstrated any honeycombing (N=5) on HRCT imaging of the whole lung, we did not examine whether the presence of this allele affected changes in the quantitative extent of honeycombing in SLS II.

DISCUSSION

To our knowledge, this is the first study to evaluate whether the presence of the *MUC5B* rs35705950 allele affects progression of ILD among SSc patients receiving treatment with MMF or CYC. The results reported herein demonstrate that this gain-of-function promoter polymorphism is not associated with radiographic or physiologic progression of ILD in patients with SSc with a predominantly non-specific interstitial pneumonia (NSIP) pattern of fibrosis on HRCT.

At baseline, the presence of the *MUC5B* allele did not discriminate between SSc-ILD clinical subgroups (i.e. limited versus diffuse; males versus females), with the exception of race. Similar to available data from the general population, this variant was quite rare among African Americans in our cohort. The implications of this racial disparity are unknown since African American and non-African American patients with SSc-ILD demonstrated similar ILD progression rates and long-term mortality outcomes in SLS II [13]. However, this may be related to the observation that the *MUC5B* allele is more predictive of an UIP phenotype [3, 5], than a NSIP phenotype of ILD. In support of this hypothesis, patients of African descent rarely develop IPF, a disease where the pathological hallmark is UIP [14].

Patients who possessed at least one copy of this allele had a similar degree of restriction on pulmonary function testing, dyspnea, cutaneous sclerosis, as well as radiographic extent of

ILD, compared with patients without this allele. To our knowledge, this is the first study to examine the relationship between *MUC5B* allele and the quantitative extent of specific patterns of radiographic fibrosis using CAD in any disease state. There were no significant associations between the extent of specific features of ILD (e.g., GGO, QLF), and the presence of this allele. Because so few patients demonstrated honeycombing in SLS II, we were unable to adequately address the question of whether the *MUC5B* allele is associated with a UIP pattern in SSc-ILD patients (Only 5 participants from the entire SLS II cohort had a UIP pattern, and among these participants, only 2 underwent MUC5B genotyping analysis and both were negative for the variant). As described above, in a large RA population, the presence of the *MUC5B* allele more robustly predicted ILD when the UIP pattern was present [5]. Moreover, examination of lung tissue in 9 patients with RA-ILD in this study demonstrated that MUC5B was present in areas of microscopic honeycombing [5]. Taken together, these findings suggest that the MUC5B promoter variant may be a risk factor for the development of UIP, and not for other ILD patterns related to connective tissue diseases, such as NSIP.

Given that the presence of the *MUC5B* allele has been associated with a better disease course in IPF [4], we examined the relationship between the presence the *MUC5B* allele and the course of ILD using different metrics of disease progression. The presence of this variant was not associated with the course of the FVC, nor the change in radiographic extent of fibrosis, ILD or GGO in either treatment arm of SLS II. These findings are consistent with a prior observational study in SSc (N=440), which demonstrated that the presence of this variant was not associated with time-to-decline lung function or diffusing capacity for carbon monoxide [7]. However, in contrast to the present study, the choice of treatment, and the timing and duration of follow-up varied in this prior study [7]. Nevertheless, the collective evidence suggests that the *MUC5B* promoter variant is unlikely to be a clinically useful predictor of response to immunosuppressive therapy in SSc-ILD patients. Given the emergence of new therapies for SSc-ILD (e.g. anti-fibrotics), it will be important to assess whether the presence of this variant affects response rates to these therapies.

The study has some notable limitations. Since these data are derived from an RCT where presence of GGO was one of the inclusion criteria, the results may not be generalizable to other SSc-ILD populations. Given that SLS II was comprised of 14-geographically distinct study centers in the US, the findings may be most applicable to US SSc-ILD patients. Second, not all SLS II participants underwent *MUC5B* genotyping, as DNA was not available in 14 patients. However, a post-hoc analysis demonstrated that there were no significant differences in the baseline characteristics of SLS II participants with and without MUC5B genotyping. Third, the diagnosis of UIP was based on radiographic criteria and not histological criteria.

Strengths of this study include the use of a clinically well-characterized and racially diverse SSc-ILD cohort. The use of a clinical trial cohort facilitated our ability to more adequately control for treatment effect and also to measure ILD progression in a standardized fashion. Using repeated measurements of the FVC to define disease progression [15] is a likely superior approach than using the change in the FVC from 2 single measurements that is

often reported in observational cohorts, given the high variability that exists in pulmonary function parameters.

While this study failed to identify associations between the presence of the *MUC5B* promoter variant and severity and progression of ILD in SSc, we caution the interpretation of these results as being "negative." In a disease with immense variation in its presentation and disease course, it is important to understand how genetic factors converge to affect SSc-ILD endotypes. This study examined a single genetic polymorphism; it is plausible that the presence of this polymorphism in combination with the presence of other polymorphisms could help us to define specific endotypes of SSc-ILD. These additional genetic analyses are currently underway using the SLS II cohort.

Characterizing ILD disease endotypes in SSc will ultimately allow us to identify patients early on who may be at heightened risk for ILD progression, who may respond preferentially to specific ILD therapies, or who may not derive a clinically meaningful benefit from upfront ILD therapy. In order to personalize the care of patients in SSc-ILD, future studies are needed that explore how specific genetic polymorphisms, such as *MUC5B*, affect disease progression in patients with SSc-ILD.

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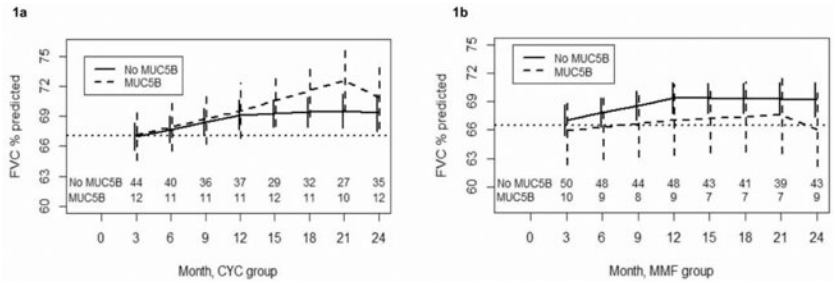

Figure 1.

Course of the FVC%-predicted from 3 to 24 months in SLS II participants with and without the MUC5B promoter variant who were randomized to CYC (A) and MMF (B). The solid line represents participants without the MUC5B promoter variant and the dotted line represents participants with the MUC5B promoter variant. The horizontal line represents the mean baseline FVC%-predicted for the entire SLS II cohort.

Table 1.

Comparison of baseline characteristics of SLS II participants based on the presence of the MUC5B promoter variant*

Measure	MUC5B Present (N=23)	MUC5B Absent (N=105)	p-value
Age, years	52.8 ± 9.0	52.0 ± 9.9	0.735
Female	18 (78.3%)	76 (72.4%)	0.563
Race			**0.032**
Caucasian	22 (95.7%)	68 (64.8%)	
Black	1 (4.4%)	26 (24.8%)	
Asian	0 (0%)	9 (8.6%)	
Other	0 (0%)	2 (1.9%)	
Diffuse	13 (56.5%)	61 (58.1%)	0.889
Disease duration, years	2.6 ± 1.7	2.6 ± 1.7	0.855
FVC, % predicted	67.1 ± 10.7	66.4 ± 9.0	0.763
FEV1/FVC, %	82.9 ± 6.2	82.4 ± 5.7	0.680
TLC, % reference	67.8 ± 11.4	65.8 ± 11.3	0.445
DLCO, % reference	52.9 ± 16.5	54.4 ± 12.4	0.614
BDI (focal score; 0-12)†	6.8 ± 1.9	7.4 ± 2.3	0.085
HAQ-DI (score, 1-3)‡	0.7 ± 0.5	0.7 ± 0.7	0.208
Modified Rodnan Skin Score (MRSS) (0-51)	12.6 ± 8.3	14.6 ± 10.3	0.480
QLF, % WL	8.4 ± 7.3	8.9 ± 7.1	0.710
QLF, % ZM	21.4 ± 20.8	24.1 ± 20.0	0.512
QILD, % WL	30.8 ± 14.4	29.3 ± 14.1	0.528
QILD, % ZM	49.9 ± 21.7	52.3 ± 20.4	0.567
QGGO% WL	22.4 ± 10.7	20.4 ± 9.0	0.349
QGGO, % ZM	32.3 ± 14.0	32.1 ± 11.2	0.950
HC, % WL > 0	0 (0%)	3 (3.0%)	1.000
HC, % ZM > 0	1 (4.4%)	4 (4.0%)	1.000
UIP pattern on HRCT	0 (0%)	2 (1.9%)	1.000

*Data reported are mean ± SD or N (%)

†High score denotes worse dyspnea

‡High score denotes worse function

Definition of abbreviations: FVC = forced vital capacity; FEV_1 = forced expired volume in 1 sec; TLC = total lung capacity; DLCO = single-breath diffusing capacity for carbon monoxide; % BDI = baseline dyspnea index; HAQ-DI = health assessment questionnaire for scleroderma-Disability Index; MRSS = Modified Rodnan Skin Score; QLF-WL, % = quantitative extent of lung fibrosis (reticulations); ZM = zone of maximal involvement on HRCT; WL = whole lung involvement on HRCT; QILD-WL, % = quantitative extent of interstitial lung disease (fibrosis + GGO + honeycombing); GGO = quantitative extent of ground glass opacities; HC = quantitative extent of honeycombing; UIP = usual interstitial pneumonia; HRCT = high-resolution computed tomography.

Table 2.

The presence of the MUC5B variant is not associated with the course of the FVC%-predicted from 3-24 months in patients randomized to CYC in SLS II.

	Estimate	95% CI	P-Value
Intercept	6.39	−0.68, 12.98	0.081
MUC5B presence	0.93	−3.24, 3.28	0.94
Baseline FVC	0.90	0.80, 1.00	<0.001
African American	−2.51	−5.26, 0.20	0.078
Time (0-12 months)	0.24	0.12, 0.37	0.001
Time (12-21 months)	−0.20	−0.48, 0.07	0.15
Time (21-24 months)	−0.11	−0.87, 0.61	0.75
MUC5B x Time (0-12)	0.03	−0.23, 0.29	0.82
MUC5B x Time (12-21)	0.26	−0.32, 0.83	0.36
MUC5B x Time (21−24)	−0.77	−2.17, 0.71	0.29

Table 3.

The presence of the MUC5B variant is not associated with the course of the FVC%-predicted from 3-24 months in patients randomized to MMF in SLS II.

	Estimate	95% CI	P-Value
Intercept	4.00	−5.68, 14.57	0.43
MUC5B presence	−0.65	−5.01, 3.44	0.77
Baseline FVC	0.94	0.78, 1.08	<0.001
African American	−1.19	−4.66, 2.50	0.51
Time (0-12 months)	0.26	0.15, 0.37	<0.001
Time (12-21 months)	−0.27	−0.49, −0.06	0.009
Time (21-24 months)	−0.03	−0.54, 0.52	0.90
MUC5B x Time (0-12)	−0.14	−0.42, 0.14	0.32
MUC5B x Time (12-21)	0.20	−0.35, 0.77	0.47
MUC5B x Time (21-24)	−0.53	−1.83, 0.77	0.44

Table 4.

Linear regression analyses evaluating the relationship between the presence of the MUC5B promoter variant and change in radiographic extent of fibrosis, ILD and ground-glass opacities from baseline to 24 months in SLS II.

2A. Outcome: QLF-WL at 24 months			
Parameter	**Estimate**	**Standard Error**	**P-Value**
MUC5B presence	−1.95	1.07	0.07
QLF-WL Baseline	0.82	0.06	<.0001
CYC arm	0.14	0.85	0.87
African American	0.09	1.08	0.93

2B. Outcome: QLF-ZM at 24 months			
Parameter	**Estimate**	**Standard Error**	**P-Value**
MUC5B presence	−2.77	2.87	0.34
QLF-ZM Baseline	0.94	0.05	<.0001
CYC arm	−0.45	2.28	0.85
African American	1.75	2.89	0.55

2C. Outcome: QILD-WL at 24 months			
Parameter	**Estimate**	**Standard Error**	**P-Value**
MUC5B presence	−2.20	2.31	0.34
QILD-WL Baseline	0.80	0.07	<.0001
CYC arm	1.35	1.84	0.46
African American	0.36	2.31	0.88

2D. Outcome: QILD-ZM at 24 months			
Parameter	**Estimate**	**Standard Error**	**P-Value**
MUC5B presence	−1.81	3.23	0.58
QILD-ZM Baseline	0.97	0.06	<.0001
CYC arm	0.06	2.57	0.98
African American	−0.37	3.28	0.91

2E. Outcome: QGGO-WL at 24 months			
Parameter	**Estimate**	**Standard Error**	**P-Value**
MUC5B presence	−0.08	1.63	0.30
QILD-ZM Baseline	0.75	0.07	0.96
CYC arm	1.41	1.29	<.0001
African American	0.49	1.61	0.76

2F. Outcome: QGGO-ZM at 24 months

2A. Outcome: QLF-WL at 24 months			
Parameter	**Estimate**	**Standard Error**	**P-Value**
Parameter	**Estimate**	**Standard Error**	**P-Value**
MUC5B presence	0.41	2.08	0.84
QILD-ZM Baseline	0.79	0.07	<.0001
CYC arm	2.08	1.65	0.21
African American	0.08	2.07	0.97