

SHORT REPORT

Assessing the *MUC5B* promoter variant in a large cohort of systemic sclerosis-associated interstitial lung disease

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ABSTRACT

Objective The common gain-of-function variant rs35705950, located in the promoter of *MUC5B* gene, has been strongly associated with interstitial lung diseases (ILDs) of different aetiology, such as idiopathic pulmonary fibrosis (IPF) and rheumatoid arthritis-associated ILD (RA-ILD). In this study, we aimed to investigate the association of this variant and its nearby single nucleotide polymorphisms (SNPs) in the largest cohort of systemic sclerosis-associated ILD (SSc-ILD) to date.

Methods Samples were collected from blood/saliva, followed by DNA extraction and genotyping using SNP arrays. Data for rs35705950 and additional 903 variants within 100 Kb were obtained using genomic imputation. Subsequently, we tested their association in a meta-analysis to increase the consistency of the results, including 10 European ancestry cohorts comprising 2363 patients with SSc-ILD, 3526 SSc patients without ILD and 15 076 controls.

Results Meta-analysis showed no significant association between rs35705950 and SSc-ILD, either comparing patients with SSc with and without ILD (p value: 0.588, OR: 1.05, 95% CI: 0.87 to 1.27) nor patients with SSc-ILD with controls (p value: 0.061, OR: 1.16, 95% CI: 0.99 to 1.36). Moreover, none of the additional 903 variants tested in the genomic region reached statistical significance.

Conclusion Despite analysing the largest and most statistically powered SSc-ILD cohort to date, we found no evidence of association between the *MUC5B* promoter variant rs35705950 and its surrounding SNPs with SSc-ILD. These results suggest that the pathogenic mechanisms underlying SSc-ILD may only partially overlap with those of other similar ILDs, such as IPF or RA-ILD. This highlights the need for further studies regarding their genetic architecture.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ *MUC5B* promoter variant rs35705950 is a well-established genetic risk factor for idiopathic pulmonary fibrosis (IPF) and rheumatoid arthritis-associated interstitial lung disease (RA-ILD).
- ⇒ Previous studies in systemic sclerosis-associated ILD (SSc-ILD) have shown no association with this functional variant, yet they might be underpowered due to their limited sample size.

WHAT THIS STUDY ADDS

- ⇒ This study confirms that the *MUC5B* promoter variant rs35705950 and its surrounding single nucleotide polymorphisms are not associated with SSc-ILD, in a well-powered cohort.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ The results of this study highlight the differences in the genetic architecture of SSc-ILD and similar ILDs as IPF and RA-ILD.
- ⇒ More research is needed regarding the genetics of SSc-ILD and other ILDs, to determine the extent of their genetic overlap.

INTRODUCTION

Systemic sclerosis-associated interstitial lung disease (SSc-ILD) is currently the leading cause of mortality in patients with SSc and is characterised by significant clinical heterogeneity and unpredictable disease progression.¹

Despite this variability, SSc-ILD shares key clinical features with other ILDs, such as idiopathic pulmonary fibrosis (IPF) and rheumatoid arthritis-associated ILD (RA-ILD), including progressive pulmonary fibrosis, declining lung function, worsening respiratory symptoms and higher mortality.² In addition to clinical overlap, these ILDs also exhibit shared genetic architecture. For instance, a variant in the *FAM13A* gene, previously associated with IPF, has recently been reported in patients with SSc-ILD presenting a usual interstitial pneumonia (UIP) pattern.³ Furthermore, both IPF and RA-ILD have been associated with rare deleterious variants in telomere-related genes such as *TERT* and *RTEL1*.⁴

In this regard, the common gain-of-function variant rs35705950, located in the promoter of the *MUC5B* gene, is the strongest genetic risk factor for IPF and is also strongly associated with RA-ILD.^{5,6} *MUC5B* encodes a mucin protein that plays a crucial role in mucus secretion across multiple organs, including the lungs.⁷ However, its exact pathogenic mechanism is not well described. Furthermore, despite the similarities among IPF, RA-ILD and SSc-ILD, no significant association has been reported for this gain-of-function variant and SSc-ILD to date.^{3,8–11} Nevertheless, previous studies have been limited by small sample sizes (ranging from 109 to 662 patients with SSc-ILD), or the use of suboptimal control groups, such as the general population rather than patients with SSc without ILD. This may have hindered the detection of a potential SSc-ILD specific association.

Given these considerations, we hypothesised that the *MUC5B* promoter variant may contribute to SSc-ILD risk in the largest well-powered cohort of patients analysed to date. To test this, we assessed the association of rs35705950 and its surrounding variants in a cohort comprising 2363 patients with SSc-ILD, 3526 patients with SSc without ILD and 15 076 controls.

MATERIALS AND METHODS

Study population

The 10 cohorts included in this study comprised a total of 2363 patients with SSc-ILD, 3526 patients with SSc without ILD and 15 076 controls. Blood/saliva samples were collected from all individuals, and, after DNA extraction, genome-wide genotyping was carried out using the arrays specified in online supplemental table S1. All individuals had European descent and were recruited from Spain, the UK, the USA, Australia, Italy, Germany, Switzerland, France and the Netherlands. All patients fulfilled the 2013 American College of Rheumatology/the European League Against Rheumatism classification criteria, or the criteria proposed by LeRoy and Medsger for early SSc.^{12,13} Clinical characteristics and further information on the 10 cohorts analysed are summarised in online supplemental table S1.

Presence or absence of ILD in patients with SSc was assessed using high-resolution CT (HRCT), or by the

presence of radiological abnormalities on chest x-ray or abnormalities on pulmonary function tests (PFTs).

Quality control and imputation of *MUC5B* relevant region

Standard and stringent single nucleotide polymorphism (SNP) array quality control (QC) measures were applied to avoid potential source of bias. Samples with genotype missingness >0.05 or ambiguous sex annotation were excluded. Furthermore, to eliminate related or duplicated individuals, we estimated identity-by-descent and excluded one individual from each pair of relatives ($Pi_Hat > 0.4$) or duplicates ($Pi_Hat > 0.99$). Additionally, variants with low call rate (< 0.98), deviations from Hardy-Weinberg equilibrium (HWE) (p value $< 1 \times 10^{-3}$) or a minor allele frequency (MAF) < 0.01 were filtered out. Palindromic SNPs with an A/T or C/G allele frequency exceeding 40% were also removed. After QC, we conducted genome-wide imputation using the TOPMed Imputation Server (<https://imputation.biodatacatalyst.nih.gov/>) and focused on the surrounding region of the *MUC5B* gain-of-function promoter variant rs35705950 (100 Kb upstream and 100 Kb downstream), comprising a total of 904 variants. We only considered SNPs with a good quality imputation (squared correlation (Rsq) > 0.3) for further analyses and excluded SNPs with MAF < 0.01 . Finally, to account for population structure, principal component analysis was conducted using PLINK and GCTA64^{14,15} for each cohort individually. 10 principal components were calculated for each cohort, and individuals deviating by more than four SD from the cluster centroid of their respective cohort were identified as outliers and removed.

Statistical analysis

Logistic regression analyses for allele dosages were conducted in PLINK for each cohort, adjusting for sex and the first five principal components in the comparison of SSc-ILD with patients with SSc without ILD, and for patients with SSc-ILD with controls. Then inverse variance weighted meta-analysis of the datasets was carried out using Metasoft¹⁶ under a fixed-effect model in variants without evidence of heterogeneity (Cochran's Q p value > 0.05), while the random effect model (RE2) was used for SNPs showing heterogeneity (Cochran's Q p value < 0.05). Statistical significance threshold was declared in all comparisons at 5.53×10^{-5} for the 904 SNPs within the region analysed, calculated using Bonferroni correction for multiple testing ($0.05/904$). Power calculations were conducted with Quanto (<https://keck.usc.edu/biostatistics/software/>) for MAF=0.05–0.45 and allele effects (OR)=1–2 (online supplemental figure 1 and online supplemental figure 2).

RESULTS

The meta-analyses revealed no significant association between the *MUC5B* promoter SNP rs35705950 and SSc-ILD. Specifically, for the comparison of SSc-ILD with SSc without ILD, the p value was 0.588 (OR: 1.05, 95% CI:

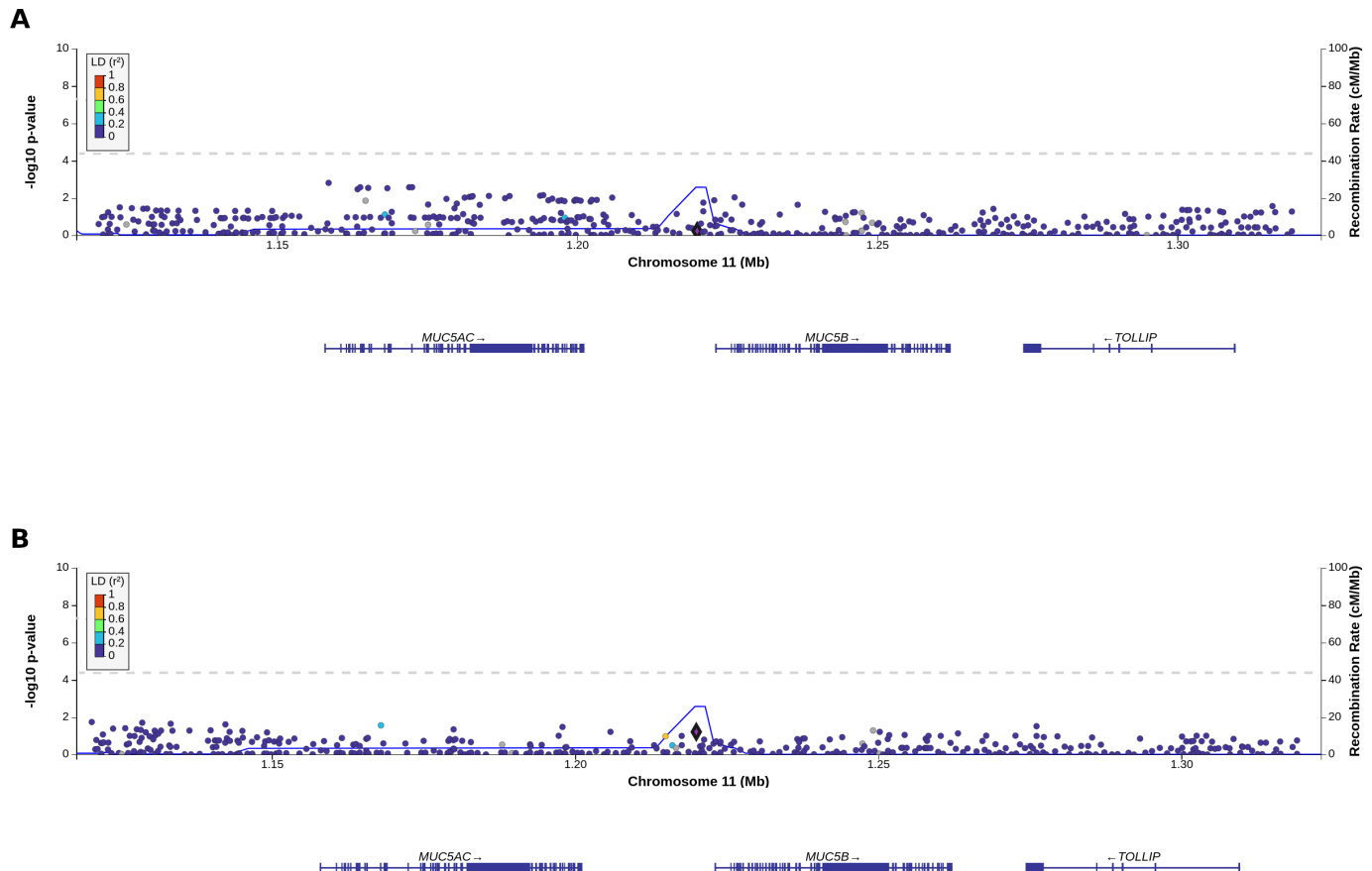


Figure 1 Locus zooms of the region surrounding the *MUC5B* rs35705950 variant. A) Locus zoom of the region surrounding rs35705950 for the comparison of SSc-ILD versus patients with SSc without ILD. Variant rs35705950 is represented as a diamond, and other SNPs as dots. The colour of the dots indicates linkage disequilibrium with rs35705950. Dashed line corresponds to 5.53×10^{-5} significance threshold. (B) Locus zoom of the region surrounding rs35705950 for the comparison of SSc-ILD versus controls. Variant rs35705950 is represented as a diamond, and other SNPs as dots. The colour of the dots indicates linkage disequilibrium with rs35705950. The dashed line corresponds to 5.53×10^{-5} significance threshold. LD, linkage disequilibrium; SNP, single nucleotide polymorphism; SSc-ILD, systemic sclerosis-associated interstitial lung disease.

0.87 to 1.27). Similarly, no significant association was observed when comparing patients with SSc-ILD with controls (p value: 0.061, OR: 1.16, 95% CI: 0.99 to 1.36). Forest plots showing the OR and 95% CI of rs35705950 for each cohort separately are available in online supplemental figure 3.

To further investigate potential associations in the genomic region, we analysed an additional 903 variants located within ± 100 Kb of the *MUC5B* promoter SNP. None of these variants reached statistical significance after multiple testing correction, suggesting a lack of association in these loci in either comparison (figure 1). The 10 most significant variants in each comparison are included in table 1 and table 2. Association data for the remaining SNPs are included in online supplemental table S2 and S3.

DISCUSSION

In this study, we investigated the association between the *MUC5B* functional promoter variant rs35705950 and SSc-ILD in the largest cohort analysed to date. Our results showed no significant association between this variant, or

any of the surrounding SNPs, and SSc-ILD. Notably, this study attained an 80% statistical power to detect associations in variants with MAF of 0.1, which is the case of the SNP rs35705950, and effect sizes of 1.35. Thus, if the promoter variant had a similar effect in SSc-ILD as it does in IPF or RA-ILD (ORs > 3.1),^{5 6} our study would have been sufficiently powered to detect it.

The findings from this work replicate the results from previous studies in SSc. More specifically, this association has been tested in the participants from Scleroderma Lung Study II clinical trial to assess its effect on SSc-ILD progression and on the clinical course of patients,⁹ as well as in SSc cohorts with low sample size (less than 670 patients with SSc-ILD),^{3 8 10 11} all of them reporting no association with the disease. These results suggest that, despite the clinical similarities, the pathogenic mechanisms underlying SSc-ILD differ from those of RA-ILD or IPF.

A previously proposed explanation for the differential association of rs35705950 across ILDs relates to the predominant histopathological pattern in each disease. The association with *MUC5B* has been consistently

Table 1 Summary statistics of *MUC5B* rs35705950 promoter variant and 10 most significant variants within 100Kb for the comparison of SSc-ILD versus SSc without ILD

SNP	Ref allele	Effect allele	Position	Nearest gene	P value	OR (CI 95%)	Model	Population frequency*
rs35705950	G	T	1219991	<i>MUC5B</i>	5.88E-01	1.05 (0.87 to 1.27)	FE	0.110
rs34582600	G	C	1 158 593	<i>MUC5AC</i>	1.55E-03	1.06 (1.02 to 1.11)	RE	0.601
rs28463198	G	C	1 158 598	<i>MUC5AC</i>	1.56E-03	1.06 (1.02 to 1.11)	RE	0.601
rs28713701	C	G	1 158 590	<i>MUC5AC</i>	1.56E-03	1.06 (1.02 to 1.11)	RE	0.601
rs996372487	A	C	1 172 511	<i>MUC5AC</i>	2.64E-03	0.96 (0.93 to 0.98)	RE	0.402
rs914303524	C	T	1 172 014	<i>MUC5AC</i>	2.67E-03	1.04 (1.02 to 1.07)	RE	0.598
rs28707071	G	C	1 163 859	<i>MUC5AC</i>	2.67E-03	1.05 (1.02 to 1.08)	RE	0.590
rs28433367	T	C	1 165 184	<i>MUC5AC</i>	2.87E-03	0.95 (0.92 to 0.98)	RE	0.413
rs28404876	C	G	1 168 378	<i>MUC5AC</i>	2.98E-03	1.04 (1.01 to 1.07)	RE	0.594
rs28373192	C	T	1 163 418	<i>MUC5AC</i>	3.39E-03	1.05 (1.02 to 1.09)	RE	0.598
rs35917282	A	G	1 165 484	<i>MUC5AC</i>	3.46E-03	0.95 (0.91 to 0.98)	RE	0.410

In boldface, the *MUC5B* promoter variant rs35705950.

Genomic position is referenced to build hg38.

*Population frequency corresponds to the frequency of the effect allele in European (non-Finnish) population from gnomAD V.4.1.0 database. FE, fixed effect; ILD, interstitial lung disease; RE, random effect; Ref, reference; SNP, single nucleotide polymorphism; SSc, systemic sclerosis.

observed in diseases like IPF and RA-ILD, all of which are primarily characterised by UIP. However, ILDs for which there is no association with this variant, as SSc-ILD or autoimmune myositis-associated ILD, present other predominant patterns as non-specific interstitial pneumonia.^{1 17 18} These findings support the hypothesis that this variant is more likely associated with the UIP pattern rather than with ILDs in general. However, a study focusing on the UIP pattern in SSc-ILD did not find an association either, although its sample size was very

limited, so further research is warranted in this subgroup of patients.³ It is worth mentioning that nominally significant variants in the surrounding region of rs35705950 are located near the *MUC5AC* gene. Given that a previous work in IPF has discussed the independent effect of both genes,¹⁹ we believe that further studies focussing on the role of *MUC5AC* in SSc-ILD are warranted.

Despite the strengths of our study, certain limitations must be acknowledged. First, we lacked the necessary data to stratify our cohort by its histopathological

Table 2 Summary statistics of *MUC5B* rs35705950 promoter variant and 10 most significant variants within 100Kb for the comparison of patients with SSc-ILD versus controls

SNP	Ref allele	Effect allele	Position	Nearest gene	P value	OR (CI 95%)	Model	Population frequency*
rs35705950	G	T	1219991	<i>MUC5B</i>	6.12E-02	1.16 (0.99 to 1.36)	FE	0.110
rs75194112	G	A	1 120 287	<i>MUC2</i>	1.81E-02	0.68 (0.49 to 0.94)	FE	0.028
rs148428215	C	G	1 128 608	<i>MUC5AC</i>	1.97E-02	0.68 (0.50 to 0.94)	FE	0.028
rs139058053	T	A	1 133 305	<i>MUC5AC</i>	2.24E-02	0.69 (0.50 to 0.95)	FE	0.028
rs118034733	G	C	1 142 329	<i>MUC5AC</i>	2.43E-02	0.69 (0.50 to 0.95)	FE	0.028
rs28403537	C	T	1 167 980	<i>MUC5AC</i>	2.72E-02	1.31 (1.03 to 1.65)	FE	0.041
rs5744025	C	T	1 276 105	<i>TOLLIP</i>	3.03E-02	1.44 (1.04 to 2.00)	FE	0.020
rs34815853	C	A	1 197 927	<i>MUC5AC</i>	3.31E-02	1.29 (1.02 to 1.63)	FE	0.044
rs34474233	G	A	1 197 926	<i>MUC5AC</i>	3.33E-02	1.29 (1.02 to 1.63)	FE	0.044
rs75900172	A	G	1 125 806	<i>MUC2</i>	3.89E-02	0.85 (0.72 to 0.99)	FE	0.126
rs72842479	C	T	1 123 799	<i>MUC2</i>	4.10E-02	0.85 (0.72 to 0.99)	FE	0.127

In boldface, the *MUC5B* promoter variant rs35705950.

Genomic position is referenced to build hg38.

*Population frequency corresponds to the frequency of the effect allele in European (non-Finnish) population from gnomAD V.4.1.0 database. FE, fixed effect; ILD, interstitial lung disease; Ref, reference; SNP, single nucleotide polymorphism; SSc, systemic sclerosis.

pattern. Given that some patients with SSc-ILD exhibit a UIP pattern, such stratification could have allowed us to detect an association specific to this subgroup, especially given the low sample size of the previous work focused on exploring rs37505950 in patients with SSc-ILD with UIP.³ Additionally, a small percentage of patients included in this study (9.6%) were not diagnosed using HRCT, as during the early period of the study this technique was ordered in the presence of risk factors such as pulmonary symptoms, radiological abnormalities on chest X-ray or physiological abnormalities on PFTs. This may have caused the misclassification of patients with SSc-ILD, mainly by underdiagnosing them.²⁰ However, as this is a small proportion of the cohort, the potential loss of statistical power may not be substantial.

In summary, despite analysing the largest and most statistically powered SSc-ILD cohort to date, we did not detect an association between the *MUC5B* promoter variant rs35705950 and the surrounding SNPs with SSc-ILD. This suggests that, for this locus, the genetic architecture and pathogenic mechanisms underlying SSc-ILD differ from those of other ILDs such as IPF or RA-ILD. However, shared genetic risk factors may still exist at other loci, underscoring the need for further genetic studies across these conditions.

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