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ORIGINAL RESEARCH

MUC5B promoter variant rs35705950, rare but significant susceptibility locus in rheumatoid arthritis-interstitial lung disease with usual interstitial pneumonia in Asian populations

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ABSTRACT

Background *MUC5B* variant rs35705950 is the common and most significant risk variant for rheumatoid arthritis-interstitial lung disease (RA-ILD) in Western populations. However, little is known about its significant association with RA-ILD in Asian populations. We here investigate the association of rs35705950 with Korean patients with RA-ILD.

Methods In this cross-sectional study, we genotyped rs35705950 in 2444 patients with RA. Among them, 683 patients with RA who have chest CT were divided into RA-ILD and RA-noILD. RA-ILD was classified as usual interstitial pneumonia (UIP) and other than UIP. The associations of rs35705950 with RA-ILD and its subtype were analysed using multivariable regression adjusted for age at RA diagnosis. Meta-analysis of a previously reported Japanese dataset and Korean dataset obtained for this study was conducted.

Results The minor allele (T) frequency of rs35705950 was 0.37%, 1.43% and 2.38% in 2444 patients with RA, 105 patients with RA-ILD and 63 patients with UIP, respectively. Genotypic association of rs35705950 with RA-ILD was insignificant (OR 2.49, 95% CI 0.64 to 9.69, p=0.187), but showed significant association with UIP (OR 4.90, 95% CI 1.23 to 19.59, p=0.024) compared with RA-noILD. In meta-analysis (123 UIP and 878 RA-noILD) combining our data with previously reported Japanese data, this variant was found to be significantly associated with UIP (OR 3.51, 95% CI 1.19 to 10.37, p=0.023).

Conclusion *MUC5B* variant rs35705950 is a rare but significant risk factor for Asian patients with RA-ILD with UIP, suggesting a sharing of the genetic background between Asian and Western populations.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In a recent multiethnic study, it has shown that the *MUC5B* promoter variant rs35705950 is common and increases the risk by 3.1-fold for developing rheumatoid arthritis-interstitial lung disease (RA-ILD).

⇒ However, rs35705950 was not significantly associated with RA-ILD in Asian populations probably due to small sample size.

WHAT THIS STUDY ADDS

⇒ We genotyped rs35705950 in 2444 patients with RA and this variant was rare in Korean population (the risk allele frequency of the rs35705950 was 0.37% and 1.43% in 2444 patients with RA and 105 RA-ILD, respectively).

⇒ However, this variant was found to be significantly associated with RA-ILD with usual interstitial pneumonia (UIP) pattern for allelic model (OR 4.76, 95% CI 1.22 to 18.60, p=0.025) and for dominant model (OR 4.90, 95% CI 1.23 to 19.59, p=0.024) and this association was confirmed through the meta-analysis by combining our data on Korean patients and previously reported data on Japanese patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We first confirmed that *MUC5B* variant rs35705950 is a significant risk factor for Asian patients with RA-ILD with UIP, suggesting a sharing of the genetic background between Asian and Western populations.

⇒ Because this variant is rare in Asian populations and a substantial amount of missing heritability exists, further analysis is required to search for novel and common risk variant in Asian patients with RA-ILD.

INTRODUCTION

Rheumatoid arthritis-interstitial lung disease (RA-ILD) and idiopathic pulmonary fibrosis (IPF) have similarities regarding

clinical features, autoimmunity and genetic susceptibility.[1 2] RA-ILD and IPF have similar clinical risk factors such as male sex, old age and smoking.[3–5] In RA-ILD, the usual interstitial pneumonia (UIP), which is a pathological pattern of IPF, is the most predominant subtype.[6–8] As the anticitrullinated cyclic peptide (anti-CCP) antibody is associated with both IPF and RA-ILD, it gives rise to shared autoimmunity, of which is correlated with lymphoid aggregates in the lung of patients with IPF.[9] In addition, RA-ILD and IPF share several susceptibility genes such as mucin 5B (*MUC5B*), telomerase reverse transcriptase (*TERT*) and surfactant protein C (*SFTPC*).[10–12]

Special attention has been given to the *MUC5B* promoter variant rs35705950 because this gene is a common variant that greatly impacts the development of both IPF and RA-ILD.[10 13] In IPF, the frequency of rs35705950 T risk allele carriers ranges from 54% to 67% in both the USA and Europe and has been known to be the strongest risk variant.[14–18] It accounts for up to 35% of risk for the development of IPF.[19] It increases the risk of developing sporadic IPF and familial IPF by up to 8.3-fold and 6.2-fold, respectively.[20] In RA-ILD, the frequency of rs35705950 T risk allele carriers ranges from 13.5% to 32.6% in the USA and Europe. A multiethnic study showed that it increases the risk by 3.1-fold for developing RA-ILD.[10]

However, the genetic traits demonstrated by this *MUC5B* variant differ based on ethnicity. Relatively low frequencies of rs35705950 T risk allele carriers have been reported for IPF in Asian populations such as those in Korea,[21] China[22] and Japan,[18] ranging from 2.2% to 6.8%, compared with that in the Western populations. The risk allele frequencies of this variant for RA-ILD in Japanese and Chinese populations have been reported as 1.1% and 2.3%, respectively.[10] No significant association between RA-ILD and rs35705950 was observed in these Asian populations.[10] However, these studies had a very small sample size. As the risk allele frequency of this variant is low in Asians, more studies with a larger sample size are needed to confirm whether there is any association between the *MUC5B* variant and RA-ILD. Thus, this study aims to identify the association of the *MUC5B* promoter variant rs35705950 with RA-ILD in Korean population, and to conduct the meta-analysis of a previously reported Asian dataset and our cohort dataset to analyse in a larger sample size.

METHODS

Study participants

This is a cross-sectional study of patients with RA. The study subjects are part of the RA cohort of Hanyang University Hospital for Rheumatic Diseases and the RA-ILD cohort of Hanyang University Guri Hospital. Baseline clinical information and blood samples in the cohorts were collected at the time of enrollment. All patients with RA fulfilled the 2010 EULAR criteria or 1987 American College of Rheumatology revised criteria for RA.[23 24]

Clinical factors

Information on the age at diagnosis of RA, sex, smoking status (never, ever and current), rheumatoid factor (RF) and anti-CCP antibody were collected from baseline clinical data of the cohorts, which could be considered as potential clinical risk factors for RA-ILD.

Taqman single nucleotide polymorphism genotyping assay

The *MUC5B* promoter variant rs35705950 was genotyped in 2444 subjects. Genomic DNA was extracted from the whole peripheral blood cells. Then, the genomic DNA was diluted to 5 ng/µL in 96-well PCR plates. TaqMan single nucleotide polymorphism (SNP) genotyping assays were obtained from Applied Biosystems (Massachusetts, the USA). The PCR was performed in 5 µL of a mixture containing 2 µL of a DNA sample, 0.125 µL of each TaqMan SNP Genotyping Assay (Thermo Fisher Scientific, USA), 2.5 µL of TaqMan Genotyping Master Mix (Thermo Fisher Scientific), and 0.375 µL of distilled water. Amplification and detection were performed using a detection system (QuantStudio 12K Flex Real-Time PCR System, Thermo Fisher Scientific). After PCR amplification, allelic discrimination is performed on the same machines (QuantStudio 12K Flex Real-Time PCR System). The allelic discrimination is an endpoint plate read. The QuantStudio 12K Flex Software was used for fluorescence measurements during the plate read. The R_n values were plotted using the signals from each well. Then, the plates were analysed using automatic or manual allele calls. There were one positive control and one negative control samples for each plate. We confirmed the clustering image with positive controls. We used intragenomic DNA samples of known genotypes for positive control.

RA-ILD evaluation and classification

RA-ILD was defined based on chest CT scans. Chest CT scans were examined and read during the clinical routine practice. For unclear readings regarding the presence of ILD or ILD patterns, a rheumatologist (YBJ) reviewed the images and medical records again and discussed them with two experienced readers (radiologist SJH and YL at Hanyang University Guri Hospital) before making the final decision. The ILD status was classified as UIP (or probable UIP), indeterminate for UIP and nonspecific interstitial pneumonia (one of the alternative diagnosis category of criteria), according to international criteria.[25] The organising pneumonia among the ILD patterns was excluded from the study because it is not irreversible.

Statistical analysis

The baseline characteristics of the patients with RA-ILD were compared with those of patients with RA without ILD (RA-noILD) using an independent Student's t-test for continuous variables and the χ^2 test for categorical variables. The genetic association study was conducted

using an allelic model (T allele vs G allele) and a dominant model (T/T+G/T vs G/G). Distributions of the rs35705950 alleles repartition reached Hardy-Weinberg equilibrium (p=1). Independent clinical risk factors for RA-ILD development were investigated first with multivariable logistic regression including factors that are assumed to be associated with an RA-ILD and factors that tends to be associated (p<0.10) in the univariate analysis. Then, multivariable logistic regression was used to estimate the adjusted ORs and 95% CIs for rs35705950 of RA-ILD after adjusting for independent clinical risk factors for RA-ILD. To show the robustness of the association between the rs35705950 and RA-ILD, we further conducted multivariable logistic regression with the rs35705950 and probable clinical risk factors suggested by previous other studies.

Meta-analysis of the previously reported dataset and our cohort dataset was performed assuming a fixed-effects model on the effect estimates in the R statistical programming language using the 'metafor (V.3.8–1)' package.[26] Juge *et al* had investigated the association of rs35705950 with RA-ILD in Japanese and Chinese patients.[10] The data on Japanese patients included the genotyping information related to both RA-ILD and RA-noILD, while the data on Chinese patients included genotype information of RA-ILD only. Thus, we used the data on Japanese patients and that derived from our present study for conducting the meta-analysis. All tests were two sided and p values of <0.05 were considered to indicate statistical significance. All statistical analyses were performed using PASW Statistics, V.17 (PASW), R statistical software, V.4.2.1. and PLINK V.2.0.

RESULTS

The characteristics of study participants

Mean age of RA diagnosis was 43.0±12.8 years and the proportion of female was 87.6% in 2444 patients with RA (table 1). Among them, 694 patients with RA had chest CT scans. Excluding 11 patients with organising pneumonia which is not irreversible, 683 patients with RA were divided into RA-ILD and RA-noILD. The proportion of RA-ILD was 15.4% (n=105/683). Of these 105, 60.0% (n=63) had UIP pattern and 40% (n=42) had other than UIP pattern (table 1). Patients with RA-ILD were older at RA diagnosis and had a higher proportion of anti-CCP antibody positivity.

We investigated the clinical risk factors for RA-ILD development. Among these factors, the age at RA diagnosis (OR=1.03, 95% CI 1.02 to 1.05, $p=1.4\times10^{-4}$) was significantly associated with RA-ILD in the multivariate model (table 1). In patients with RA-ILD with the UIP pattern, the age at RA diagnosis (OR 1.05, 95% CI 1.02 to 1.07, $p=4.8\times10^{-5}$) was also a significant clinical risk factor in our multivariate model (online supplemental table S1).

Table 1 Characteristics of study participants

	Patients with RA who have genotype data (n=2444)	Patients with RA who have chest CT*				
		Total (n=683)	RA-ILD (n=105)	RA-noILD (n=578)	P value in univariate analysis	P value in multivariable analysis
Age at RA diagnosis	43.0±12.8	45.9±13.0	50.9±12.3	45.0±13.0	1.3×10^{-5}	1.4×10^{-4}
Age at ILD diagnosis			65.7±10.7			
Sex, female	2141 (87.6)	573 (83.9)	82 (78.1)	491 (84.9)	0.079	0.807
Smoking						
Never	2025/2434 (83.2)	542/680 (79.4)	79 (75.2)	463/575 (80.5)		
Ever	221/2434 (9.1)	71/680 (10.4)	15 (14.3)	56/575 (9.7)	0.152	0.662
Current	188/2434 (7.7)	67/680 (9.8)	11 (10.5)	56/575 (9.7)	0.689	0.974
RF positivity	2058/2428 (84.8)	619/683 (90.6)	99 (94.3)	520 (90.4)	0.204	0.273
Anti-CCP antibody positivity	2097 (85.8)	610 (89.3)	101 (96.2)	509 (88.1)	0.013	0.064
ILD pattern on chest CT*						
UIP (or probable UIP)			63 (60.0)			
Other than UIP†			42 (40.0)			

Values are presented as estimated means±SD or N (%).
*Of the patients who had chest CT scans, 11 patients with organising pneumonia were excluded.
†Patients with RA-ILD with other than UIP had the following patterns on chest CT: non-specific interstitial pneumonia or indeterminate for UIP.
CCP, citrullinated cyclic peptides; noILD, without ILD; RA, rheumatoid arthritis; RA-ILD, rheumatoid arthritis-interstitial lung disease; RF, rheumatoid factor; UIP, usual interstitial pneumonia.

Table 2 Allelic association of the *MUC5B* rs35705950 SNP with RA-ILD and with RA-ILD subtypes

	n	MAF (T), %	Crude OR (95% CI)	Crude P value	Adjusted OR (95% CI)*	Adjusted P value*
Patients with RA who have genotype data	2444	0.37				
Patients with RA who have chest CT	683	0.81				
RA-noILD	578	0.69	Reference		Reference	
RA-ILD	105	1.43	2.08 (0.55 to 7.90)	0.282	2.46 (0.64 to 9.47)	0.189
UIP pattern	63	2.38	3.50 (0.92 to 13.37)	0.067	4.76 (1.22 to 18.60)	0.025
Other than UIP	42	0	NA	NA	NA	NA

*The p values and OR (95% CI) were adjusted for age at RA diagnosis, which was significant clinical factors for RA-ILD in a multivariable model that considered age at RA diagnosis, sex, smoking, RF positivity and anti-CCP antibody positivity.
CCP, citrullinated cyclic peptide; MAF, minor allele frequency; NA, not available; noILD, without ILD; RA, rheumatoid arthritis; RA-ILD, rheumatoid arthritis associated interstitial lung disease; RF, rheumatoid factor; SNP, single nucleotide polymorphism; UIP, usual interstitial pneumonia.

Muc5B promoter variant and risk of ILD

Among the study subjects (n=2444) with RA, the minor allele (T) frequency (MAF) of the *MUC5B* promoter variant was 0.37% (table 2). There were 2426, 18 and 0 wild-type (GG), heterozygous (GT) and mutant genotype (TT), respectively (table 3). Among the 683 patients with RA who had chest CT scan, the MAF of the *MUC5B* promoter variant was 0.81% and the numbers of wild-type (GG), heterozygous (GT) and mutant genotype (TT) were 672, 11 and 0, respectively (tables 2 and 3).

In the multivariable analysis adjusted for age at RA diagnosis, no significant association was observed between the *MUC5B* promoter variant and the RA-ILD for allelic model (MAF case vs control 1.43% vs 0.69%, OR 2.46, 95% CI 0.64 to 9.47, p=0.189; table 2) and for dominant model (proportion of GT genotype case vs control 2.9% vs 1.4%, OR 2.49, 95% CI 0.64 to 9.69, p=0.187; table 3) when compared with RA-noILD.

We next investigated whether ILD subtypes were associated with the *MUC5B* promoter variant in patients with RA. In the multivariable analysis adjusted for age at RA diagnosis, the *MUC5B* promoter variant was significantly associated with patients with RA-ILD with the UIP pattern, which is the most frequent pattern in RA-ILD, for allelic model (MAF case vs control 2.38% vs 0.69%, OR 4.76, 95% CI 1.22 to 18.60, p=0.025; table 2) and for dominant model (proportion of GT/TT genotype case vs control 4.8% vs 1.4%, OR 4.90, 95% CI 1.23 to 19.59, p=0.024; table 3) when compared with RA-noILD. In the multivariable analysis adjusted for possible clinical factors for RA-ILD with the UIP pattern including age at RA diagnosis, male sex, smoking, RF positivity and anti-CCP antibody positivity, this significance of the *MUC5B* promoter variant for the UIP pattern was consistently observed with similar effect size (online supplemental table S2).

In patients with RA-ILD with other than UIP pattern, the *MUC5B* genotype was all wild-type (GG) without any variant. Thus, the risk of the *MUC5B* genotype for RA-ILD with other than UIP pattern could not be calculated.

MUC5B promoter variant and risk of ILD in meta-analysis

We next performed the meta-analysis using the data for Japan patients reported by Juge *et al*[10] and the data for Korean patients obtained from this study. A total, 287 patients with RA-ILD (182 Japanese and 105 Korean) and 878 patients with RA-noILD (300 Japanese and 578

Table 3 Genotypic association of the *MUC5B* rs35705950 SNP with RA-ILD and with RA-ILD subtypes

	n	GG, n (%)	GT/TT, n (%)	Crude OR (95% CI)	Crude P value	Adjusted OR (95% CI)*	Adjusted P value*
Patients with RA who have genotype data	2444	2426 (99.3)	18/0 (0.7)				
Patients with RA who have chest CT	683	672 (98.4)	11/0 (1.6)				
RA-noILD	578	570 (98.6)	8 (1.4)	Reference		Reference	
RA-ILD	105	102 (97.1)	3 (2.9)	2.10 (0.55 to 8.03)	0.280	2.49 (0.64 to 9.69)	0.187
UIP pattern	63	60 (95.2)	3/0 (4.8)	3.56 (0.92 to 13.79)	0.066	4.90 (1.23 to 19.59)	0.024
Other than UIP	42	42 (100)	0/0	NA	NA	NA	NA

*The p values and OR (95% CI) were adjusted for age at RA diagnosis, which was significant clinical factors for RA-ILD in a multivariable model that considers age at RA diagnosis, sex, smoking, RF positivity and anti-CCP antibody positivity.
CCP, citrullinated cyclic peptide; noILD, without ILD; RA, rheumatoid arthritis; RA-ILD, rheumatoid arthritis associated interstitial lung disease; RF, rheumatoid factor; SNP, single-nucleotide polymorphism; UIP, usual interstitial pneumonia.

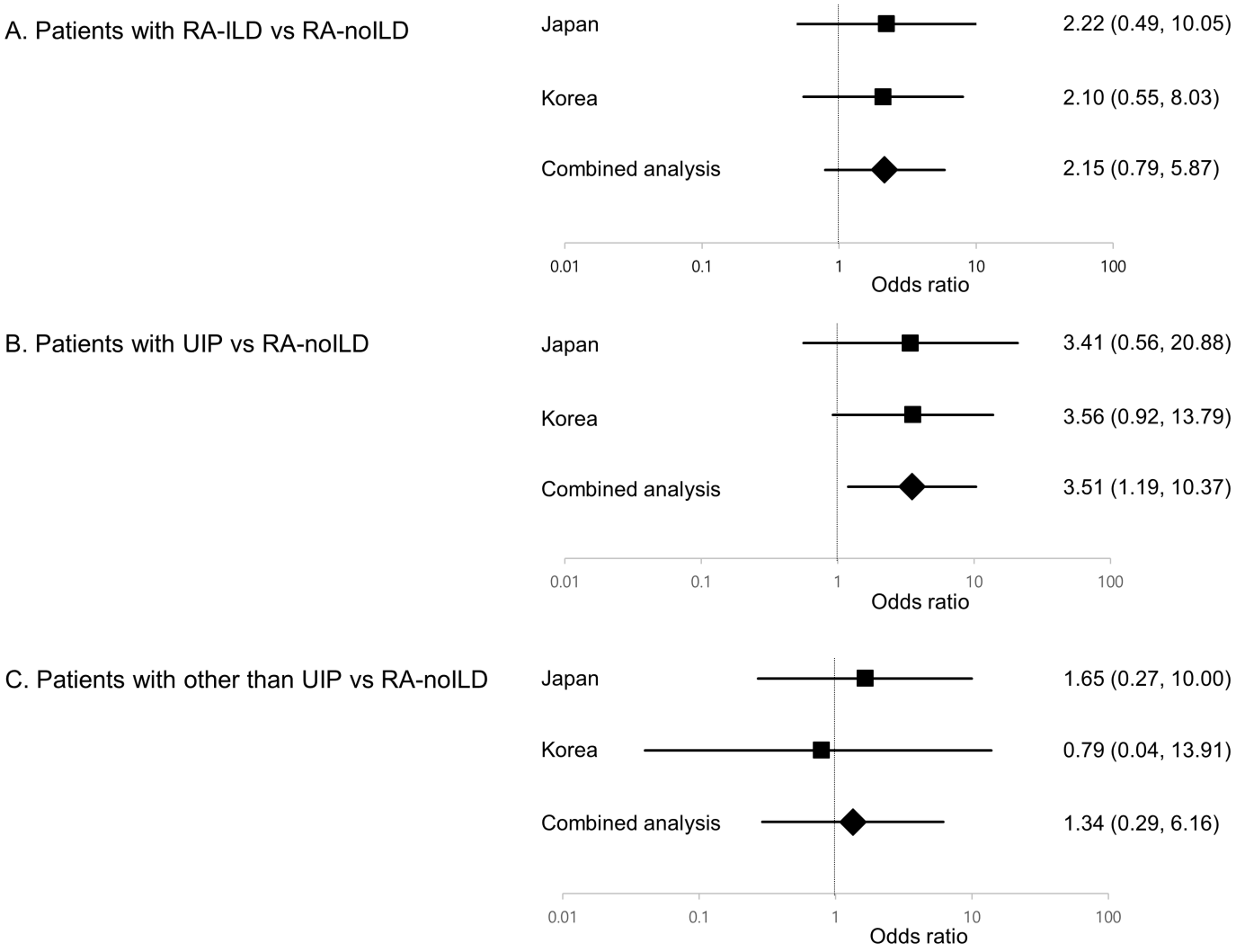

Figure 1 Association of the *MUC5B* rs35705950 promoter variant with RA-ILD in meta-analysis. Data for Japanese patients reported by Juge *et al*[10] and that for Korean patients in this study were used for the meta-analysis. Among the Japanese patients, 182 had RA-ILD (60 of whom had UIP pattern) and 300 had RA-noILD. Among the Korean patients, 105 had RA-ILD (63 of whom had UIP pattern) and 578 had RA-noILD. Because the clinical data of Japan used for adjusting factors in the previous study by Juge *et al* could not be obtained as raw data for each subject, the ORs in this meta-analysis were not adjusted with clinical variables. Figure 1A shows a genotypic association of the *MUC5B* promoter variant rs35705950 with RA-ILD. Figure 1B,C shows genotypic associations between this variant and RA-ILD with the UIP pattern and RA-ILD with other than UIP pattern, respectively. ILD, interstitial lung disease; noILD, without ILD; RA, rheumatoid arthritis; UIP, usual interstitial pneumonia.

Korean) were included in the analysis. Among them, 123 patients had RA-ILD with the UIP pattern (60 Japanese and 63 Korean). The results of the meta-analysis are shown in the forest plots of OR and 95% CIs (figure 1). The MAFs of the MUC5B promoter variant were 0.5%, 1.1% and 1.7% in Japanese patients with RA-noILD, RA-ILD and UIP, respectively (online supplemental table S3). The meta-analysis showed that the *MUC5B* genotype GT/TT was not significantly associated with RA-ILD (proportion of GT/TT genotype case vs control 2.5% vs 1.3%, OR 2.15, 95% CI 0.79 to 5.87, p=0.134) when compared with RA-noILD.

However, when the stratified analysis was conducted based on ILD subtypes, the *MUC5B* genotype GT/TT was found to be significantly associated with UIP (proportion of GT/TT genotype case vs control 4.2% vs 1.3%, OR 3.51, 95% CI 1.19 to 10.37, p=0.023) when compared with RA-noILD. No association with RA-ILD with other than UIP pattern was observed (proportion of GT/TT genotype case vs control 1.2% vs 1.3%, OR 1.34, 95% CI 0.29 to 6.17, p=0.707). Because the clinical data in the study reported by Juge *et al*[10] could not be obtained as raw data for each subject, the OR in this meta-analysis were not adjusted with clinical variables.

DISCUSSION

The MAF of the *MUC5B* variant rs35705950 was 0.37% in Korean patients with RA, 1.43% in patients with RA-ILD and 2.38% in those with UIP. These results revealed that

this variant is rare in Korean patients with RA or RA-ILD in comparison with Western patients with RA or RA-ILD (MAF=13.5–32.6%). Nevertheless, the *MUC5B* variant rs35705950 has been shown to increase the risk of UIP by 4.9-fold in Korean patients with RA.

To date, the *MUC5B* variant rs35705950 has been highlighted in terms of the common and highly significant risk gene for RA-ILD in Western populations. In contrary, this gene variant was rare, and its significant association was not shown in Asian populations. A previous multiethnic study[10] reported a MAF of only 0.5% among 300 Japanese patients with RA-noILD. Of the 182 Japanese and 22 Chinese patients with RA-ILD, the MAFs of rs35705950 were 1.1% and 2.3%, respectively. In the general Japanese population, the MAF of this variant was 0.6%.[27 28] It seems that the MAF of rs35705950 in RA-ILD tends to be higher than that of RA-noILD, and the MAF of rs35705950 in RA-noILD appears to be close to that of the general Japanese population. For Koreans, the MAF of rs35705950 has been studied in 87 Korean control subjects of IPF, and none of them had this gene variant at all.[21] Due to small sample size of Korean control subjects of IPF study, the comparison of the MAF between RA-noILD and the general Korean population needs larger sample sized control. This study is the largest one so far to investigate the *MUC5B* variant rs35705950 in patients with RA (n=2444) and we could confirm that rs35705950 is a rare variant in the Asian population.

We found that, unlike previous reports on Asian patients with RA-ILD, the *MUC5B* variant rs35705950 was a significant risk variant in Korean patients with RA-ILD with the UIP pattern. In 182 Japanese patients, the adjusted OR of the *MUC5B* variant rs35705950 for RA-ILD was 3.1 (95% CI 0.3, 28.0), but not significant (p=0.30).[10] Among 60 Japanese RA-ILD with the UIP pattern, the MAF was 1.7% and this variant was not significant either (p=0.99).[10] In 22 Chinese patients, the ORs for RA-ILD with and without UIP could not be determined because of the small proportion of carriers with risk allele or genotypes.[10] However, in this study, a significant association was observed between this variant and the UIP pattern with an OR of 4.90. This effect size is large and similar to the result obtained with French patients with RA-ILD with the UIP pattern (OR 4.9, p=0.003).[10] Additionally, our meta-analysis showed that the crude OR of the *MUC5B* variant rs35705950 for UIP was significant and similar to that obtained in Western multiethnic combined analysis (OR 3.50, $p=3.6\times10^{-7}$), although the p value in this meta-analysis was not as strong as that obtained in the Western populations.[10] To the best of our knowledge, the current study is the first to report the significant association between rs35705950 and RA-ILD with the UIP pattern in Asian population, which suggested a shared genetic background across different populations, despite marked difference in allele frequencies.

RA-ILD with the UIP pattern could be considered as a different disease entity from other types of RA-ILD. A Western multiethnic RA cohort study by Juge *et al* showed that the *MUC5B* variant rs35705950 was not associated with RA-ILD with a pattern inconsistent with UIP.[10] In addition, our study also did not show any association between this variant and RA-ILD with other than UIP pattern. This difference in genetic susceptibility between the subtypes of RA-ILD suggests different pathogenesis between UIP and other subtypes of RA-ILD and supports the concept that RA-ILD with UIP pattern is a different disease entity from other types of RA-ILD.

Notably, the clinical use of this variant might be limited because of the low frequency of the *MUC5B* variant rs35705950 T risk allele carriers in Korean patients with RA-ILD and a lack of studies on its clinical implication. However, this variant could be helpful to determine the RA-ILD subtype when radiographic classification is difficult in the chest CT scans, including the cases of suspicious early UIP pattern or of an inconclusive NSIP/UIP combination pattern. In particular, it is often difficult to determine these subtypes in the early stage of RA-ILD onset. Based on the results of our study, according to which the presence of the *MUC5B* variant rs35705950 increases the risk of RA-ILD with the UIP pattern by approximately five times, information on this variant combined with chest CT scans could increase the accuracy of diagnosis. Recently, Juge *et al* reported that the *MUC5B* variant rs35705950 could identify patients at high risk of subclinical RA-ILD.[29] In Korean patients with RA with low frequency of the *MUC5B* variant rs35705950 T risk allele carriers, further study needs to confirm the clinical implication of the *MUC5B* to identify the patients with RA with subclinical RA-ILD.

This study has several strengths and limitations. This is the first study to show a significant association between the *MUC5B* variant rs35705950 and RA-ILD with the UIP pattern in Asian patients. This was also confirmed through the meta-analysis by combining our data on Korean patients and previously reported data on Japanese patients. Although the p value showing the association between this variant and RA-ILD with the UIP pattern was not as strong as that in Western populations, the *MUC5B* variant rs35705950 was shared among Asian and Western patients with RA-ILD with the UIP pattern. As a limitation, a principal component analysis to be sure that the case and control populations were similar was not performed in the study. However, since the Korean population is a genetically homogeneous ethnic group, principal component analysis was not mandatory.

In conclusion, this study is the first to identify that the risk allele of the *MUC5B* promoter variant rs35705950 is significantly associated with Asian patients with RA-ILD with the UIP pattern. However, because this variant is rare in Asian populations and a substantial amount of missing heritability exists, further analysis is required to search for novel and common risk variant in Asian patients with RA-ILD.

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Competing interests None declared.

Patient consent for publication Not applicable.

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