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ORIGINAL RESEARCH

Association of a *FAM13A* variant with interstitial lung disease in Japanese rheumatoid arthritis

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ABSTRACT

Background Interstitial lung disease (ILD) occasionally occurs in rheumatoid arthritis (RA) and confers a dismal prognosis. We previously reported that a single-nucleotide variant (SNV) of *MUC5B* was associated with ILD in RA. However, the pathogenesis of ILD in Japanese patients with RA could not be explained solely by this SNV because its frequency is extremely low in the Japanese population. Here, we examined whether a different idiopathic pulmonary fibrosis susceptibility SNV might be associated with ILD in Japanese patients with RA.

Methods Genotyping of rs2609255 (G/T) in *FAM13A* was conducted in 208 patients with RA with ILD and 420 without chronic lung disease using TaqMan assays.

Results A significant association with usual interstitial pneumonia (UIP) in RA was detected for rs2609255 under the allele model (p=0.0092, *P*c=0.0276, OR 1.53, 95% CI 1.12 to 2.11) and recessive model for the G allele (p=0.0003, *P*c=0.0009, OR 2.63, 95% CI 1.59 to 4.32). *FAM13A* rs2609255 was significantly associated with UIP in male patients with RA (p=0.0043, OR 3.65, 95% CI 1.52 to 8.73) under the recessive model.

Conclusions This study is the first to document an association of rs2609255 with ILD in Japanese patients with RA, implicating it in the pathogenesis of UIP, though studies on the function of rs2609255 are warranted.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A single-nucleotide variant (SNV) of *MUC5B* was associated with interstitial lung disease (ILD) in rheumatoid arthritis (RA), but its frequency is extremely low in the Japanese population.

WHAT THIS STUDY ADDS

⇒ An association of *FAM13A* rs2609255 with ILD in Japanese RA was detected.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The pathogenesis of ILD in Japanese RA could be explained by the SNV in *FAM13A*, though studies on the function of the SNV are warranted.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterised by the destruction of the synovial joints. It is occasionally complicated by the development of interstitial lung disease (ILD) characterised by interstitial inflammation of the lung detected in about 10% of patients with RA.[1] The prognosis of patients with RA with ILD is quite poor.[2] Although the aetiology of RA is unclear, it is thought that disease susceptibility is associated with genetic factors, many of which have been reported for RA or idiopathic interstitial pneumonia. In contrast, only a few genetic analyses have been conducted for susceptibility to ILD in RA.

We previously reported that a single-nucleotide variant (SNV) in the *MUC5B* promoter was associated with ILD in a multiethnic study of RA.[3] This SNV has the strongest association with susceptibility to idiopathic pulmonary fibrosis.[4–8] However, the pathogenesis of ILD in Japanese patients with RA cannot be explained by this SNV because its frequency is extremely low in the Japanese population compared with European populations.[3]

RPA3-UMAD1 rs12702634 was reported to be associated with ILD in Japanese RA in a genome-wide association study (GWAS)[9] but was not confirmed in our replication study in other Japanese populations.[10] Another recent GWAS revealed that SNVs in *MUC5B*, *TOLLIP*, *FAM13A* and *TERT* genes were associated with ILD in European RA.[11] In addition to *MUC5B*, an association of *FAM13A* with idiopathic pulmonary fibrosis has been reported in GWAS or candidate gene studies.[4 7 8 12–14] *FAM13A* is also associated

Table 1 Characteristics of the patients with RA

	UIP	NSIP	ILD	CLD (–)
Number	94	114	208	420
Male, n (%)	42 (44.7)	37 (32.5)	79 (38.0)	66 (15.7)
Mean age, years (SD)	71.4 (10.0)	68.2 (10.5)	69.6 (10.4)	61.5 (12.7)

SDs or percentages are shown in parentheses.
.CLD (–), without chronic lung disease; ILD, interstitial lung disease; NSIP, non-specific interstitial pneumonia; RA, rheumatoid arthritis; UIP, usual interstitial pneumonia.

with ILD in European RA.[11] Additionally, it was reported that *FAM13A* is associated with chronic obstructive pulmonary disease.[15 16] FAM13A is expressed in the lung and is thought to be involved in the Wnt signalling pathway,[17 18] which is activated in idiopathic pulmonary fibrosis.[19 20] Thus, *FAM13A* could be a candidate susceptibility gene for ILD in RA. Accordingly, the present study was conducted to determine whether SNVs in *FAM13A* are associated with ILD in Japanese RA.

MATERIAL AND METHODS

Patients

Patients with RA fulfilled American College of Rheumatology criteria for RA[21] or Rheumatoid Arthritis Classification Criteria[22] and were recruited at the institutes of research groups organised by Tokyo National Hospital and Sagamihara National Hospital. The patients with RA were native Japanese living in Japan. Patients with RA were diagnosed with usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP) or no chronic lung disease (CLD) based on chest conventional or high-resolution CT,[23] as follows: UIP: irregular linear opacities and honeycombing, NSIP: bilateral ground-glass attenuation patterns predominantly in subpleural and basal regions, and CLD (–): no abnormalities in CT images. A total of 208 patients with RA with ILD (94 with UIP and 114 with NSIP) and 420 patients with RA without CLD were enrolled (table 1). The allele frequency of *FAM13A* rs2609255 in the Japanese population was extracted from the 38KJPN panel of the Japanese Multi Omics Reference Panel (https://jmorp.megabank.tohoku.ac.jp/202206/).[24]

Genotyping

Genotyping of rs2609255 (G/T) in the FAM13A gene was performed using a TaqMan assay (assay ID: C__15906608_10; Thermo Fisher Scientific, Waltham, Massachusetts, USA) on a 7500 Fast Real-Time PCR System (Thermo Fisher Scientific), according to the manufacturer's instructions. Conditions for thermal cycling were denaturation at 95°C for 20 s, followed by 40 cycles of 95°C for 3 s and 60°C for 30 s.

Statistical analysis

Associations of the variants were analysed to compare RA with ILD to RA without CLD by Fisher's exact test using 2×2 contingency tables under the allele model or

Table 2 Genotype frequencies of *FAM13A* rs2609255 in the patients with RA in this study

FAM13A		Genotype			Allele	Allele model				Recessive model for G allele			
rs2609255	n	(G/G)	(G/T)	(T/T)	(G)	P value	*Pc*	OR	95% CI	P value	*Pc*	OR	95% CI
UIP (+) RA, n (%)	94	32 (34.0)	35 (37.2)	27 (28.7)	99 (52.7)	0.0092	0.0276	1.53	(1.12 to 2.11)	0.0003	0.0009	2.63	(1.59 to 4.32)
NSIP (+) RA, n (%)	114	23 (20.2)	56 (49.1)	35 (30.7)	102 (44.7)	0.4969	1.0000	1.12	(0.83 to 1.50)	0.4011	1.0000	1.29	(0.76 to 2.17)
ILD (+) RA, n (%)	208	55 (26.4)	91 (43.8)	62 (29.8)	201 (48.3)	0.0400	0.1200	1.29	(1.02 to 1.63)	0.0039	0.0117	1.83	(1.22 to 2.73)
CLD (–) RA, n (%)	420	69 (16.4)	215 (51.2)	136 (32.4)	353 (42.0)								

Genotype and allele frequencies are shown in parentheses (%). Associations were tested by Fisher's exact test using 2×2 contingency tables under the allele model or the recessive model.
CLD, chronic lung disease; ILD, interstitial lung disease; NSIP, non-specific interstitial pneumonia; RA, rheumatoid arthritis; UIP, usual interstitial pneumonia.

Table 3 Genotype frequencies of *FAM13A* rs2609255 in the subpopulations of patients with RA

		Genotype			Recessive model for G allele		
	n	(G/G)	(G/T)	(T/T)	P value	OR	95% CI
Male							
UIP (+) RA, n (%)	42	19 (45.2)	17 (40.5)	6 (14.3)	0.0088	3.37	(1.43 to 7.95)
ILD (+) RA, n (%)	79	25 (31.6)	38 (48.1)	16 (20.3)	0.1299	1.89	(0.87 to 4.08)
CLD (–) RA, n (%)	66	13 (19.7)	37 (56.1)	16 (24.2)			
Age >65							
UIP (+) RA, n (%)	76	29 (38.2)	25 (32.9)	22 (28.9)	0.0016	2.62	(1.46 to 4.72)
ILD (+) RA, n (%)	152	48 (31.6)	57 (37.5)	47 (30.9)	0.0082	1.96	(1.19 to 3.23)
CLD (–) RA, n (%)	189	36 (19.0)	102 (54.0)	51 (27.0)			
Male, age >65							
UIP (+) RA, n (%)	39	18 (46.2)	16 (41.0)	5 (12.8)	0.0407	3.29	(1.10 to 9.84)
ILD (+) RA, n (%)	67	24 (35.8)	31 (46.3)	12 (17.9)	0.1592	2.14	(0.77 to 5.98)
CLD (–) RA, n (%)	29	6 (20.7)	17 (58.6)	6 (20.7)			

Genotype frequencies are shown in parentheses (%). Associations were tested in comparison with the CLD(-) RA population by Fisher's exact test using 2x2 contingency tables under the recessive model.
CLD, chronic lung disease; ILD, interstitial lung disease; RA, rheumatoid arthritis; UIP, usual interstitial pneumonia.

recessive model. The Bonferroni method was used for the adjustment of multiple comparisons; that is, p values were multiplied by the number of tests used for the calculation of corrected p values (*Pc*). Statistical power of 80% was obtained when the OR was 1.59 (UIP vs CLD (−)), 1.54 (NSIP vs CLD (−)) and 1.41 (ILD vs CLD (−)) or higher under the allele model. It was also calculated to be 2.19 (UIP vs CLD (−)), 2.08 (NSIP vs CLD (−)) and 1.82 (ILD vs CLD (−)) under the recessive model for the G allele of rs2609255 (http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize).[25] Meta-analysis in the allele model for ILD in RA was performed with EZR under the fixed effect model (http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html).[26]

RESULTS

Association of *FAM13A* rs2609255 with UIP or ILD in RA

FAM13A rs2609255 was genotyped in the patients with RA. No deviation from the Hardy-Weinberg equilibrium was observed (p=0.7683). It was investigated whether *FAM13A* rs2609255 was associated with UIP, NSIP or ILD in RA. A significant association with UIP was detected for *FAM13A* rs2609255 under the allele model (p=0.0092, *Pc*=0.0276, OR 1.53, 95% CI 1.12 to 2.11; table 2) and the recessive model for the G allele (p=0.0003, *Pc*=0.0009, OR 2.63, 95% CI 1.59 to 4.32). However, no association with NSIP was detected. *FAM13A* rs2609255 was also significantly associated with ILD in RA (p=0.0039, *Pc*=0.0117, OR 1.83, 95% CI 1.22 to 2.73) under the recessive model for the G allele. To exclude any effects resulting from differences in the male:female ratio between UIP and CLD (−) groups, the association of *FAM13A* rs2609255 was analysed solely in male patients with RA. It was found that *FAM13A* rs2609255 was significantly associated with UIP in male patients with RA (p=0.0088, OR 3.37, 95% CI 1.43 to 7.95; table 3) under the recessive model for the G allele, but it was not associated with ILD. *FAM13A* rs2609255 was also significantly associated with UIP in patients with RA older than 65 (p=0.0016, OR 2.62, 95% CI 1.46 to 4.72; table 3) under the recessive model. *FAM13A* rs2609255 was also significantly associated with UIP in male patients with RA older than 65 (p=0.0407, OR 3.29, 95% CI 1.10 to 9.84; table 3) under the recessive model. Thus, an association of *FAM13A* rs2609255 with UIP was detected in Japanese RA and a role for this variant especially in male and older patients with RA was suggested. Meta-analysis of data from previous reports[3 11] and our data confirmed a significant association with ILD in RA (p=0.0168, OR 1.24, 95% CI 1.04 to 1.49). The lack of heterogeneity was confirmed in these data (p=0.0674). Finally, we tested whether *FAM13A* rs2609255 is associated with RA itself and found that it is (p=0.0375, OR 1.13, 95% CI 1.01 to 1.26; online supplemental table S1).

DISCUSSION

Here, we found that rs2609255G is a risk allele for UIP or ILD in Japanese RA. It was also determined that *FAM13A* rs2609255 was significantly associated with UIP in male and older patients with RA, as well as an association of *FAM13A* rs2609255 generally with RA. This had already been reported in European populations,[11] but to the best of our knowledge, the present study is the first in Asian populations.

MUC5B rs35705950 was reported to be associated with ILD in RA.[3] However, the frequency of the rs35705950T risk allele is extremely low in Japanese. The predominant pathogenesis of ILD in Japanese RA therefore cannot be explained by this SNV. Other genetic factors

were suspected to be associated with ILD in Japanese RA. *RPA3-UMAD1* rs12702634 was reported to be associated with ILD in the GWAS of Japanese RA,[9] but the association described in that study was not confirmed in our replication study in other Japanese populations,[10] suggesting heterogeneity of ILD in RA. The confirmation of the results of genetic association studies by replication is important to establish their validity. The present study indicated that *FAM13A* rs2609255 is associated with UIP in Japanese RA. *FAM13A* rs2609255 was apparently associated with UIP in male and older patients with RA. However, *FAM13A* rs2609255 was not associated with NSIP in Japanese RA. Additionally, older men are predominant in RA with UIP but not in RA with NSIP.[23 27] These data suggest that the pathogenesis of ILD in RA is heterogeneous.

In a recent GWAS, *FAM13A* was associated with ILD in European RA.[11] This SNV had already been tested in a previous study in European and Mexican populations[3]; it was not associated with ILD in RA. In the present study, this association was confirmed in Japanese populations, establishing a clear genetic association. It was reported that *FAM13A* is expressed in the lungs,[17] and expression quantitative trait loci analysis in the Genotype-Tissue Expression portal database revealed an association of *FAM13A* rs2609255 with the expression of the gene in lung or tibial artery (https://gtexportal.org/home/snp/rs2609255).[28] It was reported that FAM13A modulated Wnt signalling,[17 18] which is thought to be involved in the pathogenesis of idiopathic pulmonary fibrosis.[19 20] Thus, *FAM13A* rs2609255 would be a candidate for pathogenicity in the development of ILD in RA.

To the best of our knowledge, this is the first report of an association of *FAM13A* rs2609255 with ILD in Asian RA. The study does have several limitations. The sample size was modest and the study was based on the results solely from Japanese populations. This study did not include replications in other Asian populations, though this is the replication of the European report.[11] Thus, larger scale multiethnic studies with other populations including other Asians should be performed to validate the aetiology of ILD in RA. Future studies on the function of *FAM13A* rs2609255 on ILD in RA are warranted to reveal the causality. The associations of *FAM13A* rs2609255 with the severity, progression or prognosis of ILD in patients with RA should be focused in future analyses, though it was not able to be assessed in the present study. This study established an association of *FAM13A* rs2609255 with ILD in RA, especially in older men, suggesting an explanation for the pathogenesis of ILD in Japanese RA.

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Contributors HF and STo designed the study. TH, SO and HF conducted the experiments. TH and HF analysed the data. HF, KSh, STs, SI, AO, MK, KSa, SS, TM, KM, SN and STo contributed to the collection of clinical information and materials. TH, HF and STo wrote the manuscript. HF is the guarantor

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the research ethics committee of Tokyo National Hospital (190010), Sagamihara National Hospital and all other institutes participating in the present study. Written informed consent was obtained from all participants. This study was conducted in accordance with the principles expressed in the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data supporting the findings of this study are presented in the paper and the supplementary file. Other data are available from the authors upon reasonable request. However, the clinical information and genotype data of each participant are not available under the conditions of informed consent mandated by the Act on the Protection of Personal Information.

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