RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

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

Takashi Higuchi,[1,2] Shomi Oka,[1,3] Hiroshi Furukawa ,[1,3] Kota Shimada,[4,5] Shinichiro Tsunoda,[6,7] Satoshi Ito,[8] Akira Okamoto,[9] Masao Katayama,[10] Koichiro Saisho,[11,12] Satoshi Shinohara ,[13] Toshihiro Matsui,[3,5] Kiyoshi Migita,[14,15] Shouhei Nagaoka,[16] Shigeto Tohma[1,3]

**To cite:** Higuchi T, Oka S, Furukawa H, *et al*. Association of a *FAM13A* variant with interstitial lung disease in Japanese rheumatoid arthritis. *RMD Open* 2023;**9**:e002828. doi:10.1136/rmdopen-2022-002828

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2022-002828).

**Dr. Okamoto is deceased.**

Received 29 October 2022
Accepted 9 January 2023



For numbered affiliations see end of article.

**Correspondence to**
Dr Hiroshi Furukawa;
furukawa-tky@umin.org

## 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.

**Author affiliations**
[1]Department of Clinical Research, National Hospital Organization Tokyo National Hospital, Kiyose, Japan
[2]Department of Nephrology, Ushiku Aiwa General Hospital, Ushiku, Japan
[3]Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagamihara National Hospital, Sagamihara, Japan
[4]Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center, Fuchu, Japan
[5]Department of Rheumatology, National Hospital Organization Sagamihara National Hospital, Sagamihara, Japan
[6]Department of Nephrology, Sumitomo Hospital, Osaka, Japan
[7]Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan
[8]Department of Rheumatology, Niigata Rheumatic Center, Shibata, Japan
[9]Department of Rheumatology, National Hospital Organization Himeji Medical Center, Himeji, Japan
[10]Department of Internal Medicine, National Hospital Organization Nagoya Medical Center, Nagoya, Japan
[11]Tanimura Hospital, Nobeoka, Japan
[12]Department of Orthopedics/Rheumatology, National Hospital Organization Miyakonojo Medical Center, Miyakonojo, Japan
[13]Tochigi Rheumatology Clinic, Utsunomiya, Japan
[14]Department of Gastroenterology and Rheumatology, Fukushima Medical University School of Medicine, Fukushima, Japan
[15]Clinical Research Center, National Hospital Organization Nagasaki Medical Center, Omura, Japan
[16]Department of Rheumatology, Yokohama Minami Kyosai Hospital, Yokohama, Japan

**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

**Funding** The work was supported by research grants from the following pharmaceutical companies: Teijin Pharma, Takeda Pharmaceutical Company, Pfizer Japan, Merck Sharp and Dohme, Mitsuibishi Tanabe Pharma Corporation, Eisai Co., Chugai Pharmaceutical Co., Astellas Pharma, Abbott Japan Co. and Bristol-Myers K.K; RA clinical Investigation grant from Bristol-Myers Squibb Co.; research Grants from Mitsui Sumitomo Insurance Welfare Foundation, Takeda Science Foundation, the Nakatomi Foundation, Daiwa Securities Health Foundation and Japan Research Foundation for Clinical Pharmacology; grants-in-aid for clinical research from the National Hospital Organization, the Practical Research Project for Allergic Diseases and Immunology (Research on Allergic Diseases and Immunology) from Japan Agency for Medical Research and Development, Health and Labour Science Research Grants from the Ministry of Health, Labour, and Welfare of Japan, Scientific Research (B, C) (26293123, 22591090, 15K09543 and 18K08402) from the Japan Society for the Promotion of Science.

**Competing interests** STo received honoraria from Pfizer Japan, Ono Pharmaceutical Co., Mitsubishi Tanabe Pharma Corporation, Chugai Pharmaceutical Co., Astellas Pharma, AbbVie GK and Asahi Kasei Pharma Corporation, and was supported by research grants from Teijin Pharma, Takeda Pharmaceutical Company, Pfizer Japan, Mitsubishi Tanabe Pharma Corporation, Merck Sharp and Dohme, Eisai Co., Chugai Pharmaceutical Co., Astellas Pharma and Abbott Japan Co. HF received honoraria from Takeda Pharmaceutical Company, Pfizer Japan, Luminex Japan Corporation, Dainippon Sumitomo Pharma Co., Daiichi Sankyo Co., Ayumi Pharmaceutical Corporation and Ajinomoto Co., and was supported by research grants from Bristol-Myers-Squibb Co., Mitsui Sumitomo Insurance Welfare Foundation established by Mitsui Sumitomo Insurance Co., Daiwa Securities Health Foundation established by Daiwa Securities Group, Nakatomi Foundation established by Hisamitsu Pharmaceutical Co., Takeda Science Foundation supported by Takeda Pharmaceutical Company and Japan Research Foundation for Clinical Pharmacology run by Daiichi Sankyo.

**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.

**ORCID iDs**
Hiroshi Furukawa http://orcid.org/0000-0003-1353-8056
Satoshi Shinohara http://orcid.org/0000-0001-8850-0859

## REFERENCES

1 Furukawa H, Oka S, Shimada K, *et al*. Association of human leukocyte antigen with interstitial lung disease in rheumatoid arthritis: a protective role for shared epitope. *PLoS ONE* 2012;7:e33133.
2 Koduri G, Norton S, Young A, *et al*. Interstitial lung disease has a poor prognosis in rheumatoid arthritis: results from an inception cohort. *Rheumatology (Oxford)* 2010;49:1483–9.
3 Juge P-A, Lee JS, Ebstein E, *et al*. Muc5B promoter variant and rheumatoid arthritis with interstitial lung disease. *N Engl J Med* 2018;379:2209–19.
4 Fingerlin TE, Murphy E, Zhang W, *et al*. Genome-Wide association study identifies multiple susceptibility loci for pulmonary fibrosis. *Nat Genet* 2013;45:613–20.
5 Seibold MA, Wise AL, Speer MC, *et al*. A common MUC5B promoter polymorphism and pulmonary fibrosis. *N Engl J Med* 2011;364:1503–12.
6 Noth I, Zhang Y, Ma S-F, *et al*. Genetic variants associated with idiopathic pulmonary fibrosis susceptibility and mortality: a genome-wide association study. *Lancet Respir Med* 2013;1:309–17.
7 Allen RJ, Porte J, Braybrooke R, *et al*. Genetic variants associated with susceptibility to idiopathic pulmonary fibrosis in people of european ancestry: a genome-wide association study. *Lancet Respir Med* 2017;5:869–80.
8 Hobbs BD, Putman RK, Araki T, *et al*. Overlap of genetic risk between interstitial lung abnormalities and idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2019;200:1402–13.
9 Shirai Y, Honda S, Ikari K, *et al*. Association of the RPA3-UMAD1 locus with interstitial lung diseases complicated with rheumatoid arthritis in Japanese. *Ann Rheum Dis* 2020;79:1305–9.
10 Higuchi T, Oka S, Furukawa H, *et al*. Lack of association of rs12702634 in *rpa3-UMAD1* with interstitial lung diseases in japanese rheumatoid arthritis patients. *Biomark Insights* 2022;17:11772719221091758.
11 Jönsson E, Ljung L, Norrman E, *et al*. Pulmonary fibrosis in relation to genetic loci in an inception cohort of patients with early rheumatoid arthritis from northern Sweden. *Rheumatology (Oxford)* 2022;61:943–52.
12 Hirano C, Ohshimo S, Horimasu Y, *et al*. FAM13A polymorphism as a prognostic factor in patients with idiopathic pulmonary fibrosis. *Respir Med* 2017;123:105–9.
13 Guzmán-Vargas J, Ambrocio-Ortiz E, Pérez-Rubio G, *et al*. Differential genomic profile in *tert, DSP*, and *fam13a* between COPD patients with emphysema, IPF, and CPFE syndrome. *Front Med (Lausanne)* 2021;8:725144.
14 Peljto AL, Selman M, Kim DS, *et al*. The MUC5B promoter polymorphism is associated with idiopathic pulmonary fibrosis in a mexican cohort but is rare among asian ancestries. *Chest* 2015;147:460–4.
15 Cho MH, Boutaoui N, Klanderman BJ, *et al*. Variants in FAM13A are associated with chronic obstructive pulmonary disease. *Nat Genet* 2010;42:200–2.
16 Cho MH, McDonald M-L, Zhou X, *et al*. Risk loci for chronic obstructive pulmonary disease: a genome-wide association study and meta-analysis. *Lancet Respir Med* 2014;2:214–25.
17 Jiang Z, Lao T, Qiu W, *et al*. A chronic obstructive pulmonary disease susceptibility gene, FAM13A, regulates protein stability of β-catenin. *Am J Respir Crit Care Med* 2016;194:185–97.
18 Jin Z, Chung JW, Mei W, *et al*. Regulation of nuclear-cytoplasmic shuttling and function of family with sequence similarity 13, member A (FAM13A), by B56-containing pp2as and Akt. *Mol Biol Cell* 2015;26:1160–73.
19 Chilosi M, Poletti V, Zamò A, *et al*. Aberrant Wnt/beta-catenin pathway activation in idiopathic pulmonary fibrosis. *Am J Pathol* 2003;162:1495–502.
20 Henderson WR Jr, Chi EY, Ye X, *et al*. Inhibition of wnt/beta-catenin/CREB binding protein (CBP) signaling reverses pulmonary fibrosis. *Proc Natl Acad Sci U S A* 2010;107:14309–14.
21 Arnett FC, Edworthy SM, Bloch DA, *et al*. The American rheumatism association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–24.
22 Aletaha D, Neogi T, Silman AJ, *et al*. 2010 rheumatoid arthritis classification criteria: an American College of rheumatology/european League against rheumatism collaborative initiative. *Arthritis Rheum* 2010;62:2569–81.
23 Oka S, Furukawa H, Shimada K, *et al*. Association of human leukocyte antigen alleles with chronic lung diseases in rheumatoid arthritis. *Rheumatology (Oxford)* 2016;55:1301–7.
24 Tadaka S, Hishinuma E, Komaki S, *et al*. JMorp updates in 2020: large enhancement of multi-omics data resources on the general Japanese population. *Nucleic Acids Res* 2021;49:D536–44.
25 Dupont WD, Plummer WD. Power and sample size calculations. A review and computer program. *Control Clin Trials* 1990;11:116–28.
26 Kanda Y. Investigation of the freely available easy-to-use software " EZR " for medical statistics. *Bone Marrow Transplant* 2013;48:452–8.
27 Kakutani T, Hashimoto A, Tominaga A, *et al*. Related factors, increased mortality and causes of death in patients with rheumatoid arthritis-associated interstitial lung disease. *Mod Rheumatol* 2020;30:458–64.
28 GTEx Consortium. The genotype-tissue expression (gtex) project. *Nat Genet* 2013;45:580–5.