Basic science

A genome-wide association study identifying single nucleotide polymorphisms in the *PPFIBP2* gene was predictive for interstitial lung disease in rheumatoid arthritis patients

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Abstract

Objective: Genetic polymorphisms might serve as useful prognostic markers for the timely diagnosis of RA. The purpose of this study was to identify genomic factors predictive of the occurrence of interstitial lung disease (ILD) in RA by performing a genome-wide association study of genetic variants, including single nucleotide polymorphisms (SNPs).

Methods: The study population included 306 RA patients. All patients were treated with conventional DMARDs, including 6–16 mg MTX per week. Clinical data and venous blood samples were collected from all patients before administration of DMARDs. A total of 278 347 SNPs were analysed to determine their association with ILD occurrence.

Results: Several SNPs were strongly associated with ILD occurrence (*P < 10^{-5}). rs6578890, which is located on chromosome 11 in the intronic region of the gene encoding tyrosine phosphatase receptor type F polypeptide-interacting protein-binding protein 2 (*PPFIBP2*), showed the strongest association with ILD occurrence (odds ratio 4.32, *P = 10^{-7.93}).

Conclusion: *PPFIBP2* could be a useful genetic marker for occurrence of interstitial pneumonia in RA patients and might help to identify the risk of ILD occurrence before RA treatment, thereby improving patient outcomes.

Lay Summary

What does this mean for patients?

Interstitial lung disease (ILD), or non-infectious pneumonia, belongs to a class of lung diseases commonly characterized by thickening and scarring of tissue. ILD can lead to morbidity and mortality owing to problems with gas exchange between the lungs and the blood. Genetic polymorphisms, which are variations in DNA sequences between different people, might serve as a predictive marker of disease and help with faster diagnosis. A recent study reported that variations in the *MUC5B* gene were associated with ILD in rheumatoid arthritis patients worldwide. However, the genetic background was different among different populations. We tried to identify predictive markers of ILD in Japanese rheumatoid arthritis patients. We used a genome-wide association study to search for small variations in people’s DNA. We found that a variation of the *PPFIBP2* gene had the strongest association with ILD occurrence. Testing for this variation might help doctors to identify ILD occurrence before treatment for rheumatoid arthritis, which could improve patient outcomes.

Keywords: genome-wide screening, RA, interstitial lung disease, single nucleotide polymorphisms, *PPFIBP2*
Introduction

Interstitial lung disease (ILD) or non-infectious pneumonia belongs to a class of diffuse lung diseases and represents a group of lung diseases commonly characterized by pulmonary fibrosis or progressive alveolar interstitial sclerosis that can lead to morbidity and mortality owing to respiratory insufficiency [1]. Pulmonary fibrosis is caused by several factors, including exposure to environmental pollutants, such as smoking and inhalation of particulate matter, drug toxicity, radiation exposure, collagen-related vascular diseases and genetics [2, 3]. Smoking is regarded as a major associated risk factor for the development of ILD [1]. A nationwide cohort study demonstrated that smokers had a 1.66-fold increased risk of ILD in comparison to non-smokers [4].

Idiopathic pulmonary fibrosis is the most severe type of ILD. Interestingly, lung transplantation used to be the only available treatment option [1]. Recently, the INBUILD trial demonstrated that nintedanib, an intracellular inhibitor of tyrosine kinases, slowed the rate of decline in forced vital capacity in subjects with progressive fibrosing ILDs [5]. Additionally, the SENSCIS trial demonstrated that nintedanib has antifibrotic and antiinflammatory effects in ILD associated with SSc [6]. These trials suggest that new drug treatments using antifibrotics might be beneficial to treat ILD. Seibold et al. [7] reported that a promoter variant in MUC5B (rs35705950) was expressed in nearly 50–60% of patients with ILD and was associated with a 6-fold and 20-fold increased risk of ILD for heterozygotes and homozygotes, respectively.

RA is an autoimmune disease characterized by chronic inflammation of the synovial lining of the joints, progressive joint destruction and systemic complications [8, 9]. The prevalence of RA is estimated to range between 0.5 and 1.0% in the general population [8]. As an autoimmune disease, 70–80% of RA patients produce autoantibodies, such as RF and anti-CCP antibodies [10].

Genetic polymorphisms might serve as useful prognostic markers for the timely diagnosis of RA [11]. The International HapMap Project, which has identified variations in the human genome [12], has facilitated the undertaking of genome-wide association studies (GWASs) of genetic variants, including single nucleotide polymorphisms (SNPs) [13]. For example, GWASs have helped in the identification of PADI4 as a non-MHC genomic locus predictive of RA in the Japanese population [12]. A recent study reported that the MUC5B promoter variant rs35705950 is associated with ILD (specifically, with interstitial pneumonia (IP)) in RA patients worldwide, including Japanese patients, based on high-resolution chest CT results [14]. The MUC5B promoter polymorphism rs35705950 and shorter telomere length are associated with the extent of fibrosis in ILD, while shorter telomere length alone is associated with histopathology findings typical of usual interstitial pneumonia (UIP) and reduced survival in patients with ILD [15]. However, obtaining high-quality imputation results for the MUC5B variant has been challenging because of the rare minor allele frequency, which has been estimated at 0.006 in our population-specific imputation reference panel for Japanese patients [16]. Recently, Shirai et al. [17] reported that the variant rs12702634 in RPA3-UMAD1 is associated with a relatively high RA-ILD risk in CT-confirmed fibrosis. However, a follow-up replication study by Higuchi et al. [18] demonstrated no association between rs12702634 and RA-ILD in Japanese patients.

The purpose of this study was to identify genomic factors predictive of ILD occurrence in RA patients by performing a GWAS of genetic variants, including SNPs.

Methods

Ethics statement and patient consent

This study complies with the Declaration of Helsinki, and the study protocols were approved by the ethics committee of the Research Institute of Joint Disease, Kobe, and Kobe University Graduate School of Medicine on 11 July 2004. All methods were performed in accordance with the relevant guidelines and regulations of the ethics committees. Informed consent for participation in the study was obtained from the patients before collection of blood samples for genetic analysis.

Patients

This is a retrospective cohort study. Overall, 1862 RA patients who were treated at Matsubara Mayflower Hospital from January 2005 until March 2018 were screened. All patients included in the study met the ACR 1987 revised criteria for RA [19]. Patients for whom blood samples were not collected were excluded from this study. The complete genetic data of 306 patients in the patient registry were analysed. All clinical data and blood samples were collected before any treatment, including treatment with MTX, was started. The patients in this cohort had undergone conventional or high-resolution lung CT, a common practice in the clinic for patients with respiratory symptoms. The average duration of RA was 10.9 years for RA-ILD patients and 10.3 years for non-RA-ILD patients as of March 2018. The ILD status of each subject was determined using CT imaging and classified as UIP, probable UIP or non-specific interstitial pneumonia (NSIP) according to the international criteria [20]. Based on the CT image patterns, UIP, probable UIP and NSIP were defined as RA-ILD (Fig. 1). ILD was diagnosed by two radiologists and one pulmonologist. In the few cases in which the physician’s reviews and the radiologist’s reports did not agree, the physician re-examined the chest CT images, taking into consideration the radiologist’s reports. Besides CT findings, a clinical diagnosis of RA-ILD was also confirmed by referring to medical records. Overall, 57 patients were diagnosed with ILD: 25 patients were assigned in the UIP or probable UIP group and 32 patients in the NSIP group.

All patients were treated with conventional DMARDs, including MTX. MTX doses ranged from 6 to 16 mg/week; dose increases from 6–8 to 16 mg/week followed the Japan College of Rheumatology guideline for the use of MTX in RA patients [21, 22]. Folic acid supplements were administered to all patients treated with MTX; a folic acid tablet was administered the day after MTX treatment. All DNA samples were included in the Japanese GWAS analysis.

Genome-wide SNP analysis and association study

Samples of 7 ml of venous blood were obtained into glass tubes and kept at 4°C until DNA extraction at Mitsubishi BCL. DNA samples were prepared using the GENTRA PUREGENE DNA isolation kit according to the manufacturer’s protocol (catalogue no. 158489; Quiagen, Germany).
DNA integrity was assessed using a Nanodrop 2000 spectrophotometer (Thermo Scientific, USA) to determine the ratio of optical density at 260 nm/280 nm and the concentration of total DNA. Genome-wide SNP genotyping was performed by deCode Genetics (Reykjavik, Iceland) using the Illumina HumanHap300K chip technology (Illumina, San Diego, CA). The genotyping of 317 503 SNPs was performed, including a quality control analysis. SNP genotyping was conducted using Infinium OmniExpressExome-8 Bead Chip Kit (catalogue no. 20024676; Illumina) according to the manufacturer’s protocol. SNP genotyping, calling and quality control of samples and SNPs were performed using Illumina GenomeStudio v.2011 software and a cluster file. Genotypes were scored using the GenomeStudio software and GenCall threshold of 0.15. Samples with call rates of >98% were accepted. SNPs were excluded using the following quality control criteria: \( R \text{mean} \leq 0.25; \) Cluster Sep values \( < 0.4 \); or number of no call values \( > 2 \) on all chromosomes except chromosome Y. After exclusion, 278 347 SNPs were retained for case–control analysis.

**Statistical analysis**

The demographic and clinical characteristics of the patients assigned to the ILD (57 patients) and non-ILD (249 patients) groups were compared using the Mann–Whitney U test (e.g. age and RA duration), and contingency tables for categorical data were compared using Fisher’s exact test (i.e. gender). The frequency of major allelic combinations was compared using Fisher’s exact test between ILD and non-ILD patients. Bonferroni’s correction was used for multiple comparisons.

**Results**

**Patient characteristics**

There was no significant difference in disease duration, average stage and class of Steinbrocker classification, and laboratory results, including white blood cell counts, lactate dehydrogenase levels and CRP levels between the ILD and non-ILD groups (Table 1). However, the average age \( (P = 0.004) \), gender (percentage of male patients; \( P < 0.001 \)) and average KL-6 (a mucinous glycoprotein expressed on type II pneumocytes; \( P = 0.037 \)), RF \( (P = 0.012) \) and CCP antibody \( (P = 0.008) \) titres were significantly different between the two groups (Table 1).

**Genetic association between SNPs and ILD occurrence**

Several SNPs strongly correlated with ILD occurrence were identified \( (P < 10^{-5}) \); Table 2). These SNPs included the major homozygous allele SNPs: rs6578890, located on chromosome 11 in the intronic region of PPFIBP2 \( (P = 10^{-7.93}) \); rs9804373, on chromosome 10 in the intergenic region of RPA2P2/LOC105378390 \( (P = 10^{-5.42}) \); rs9320420, on chromosome 6 in the intergenic region of LOC100287612/MARCKS \( (P = 10^{-5.41}) \); rs2116538, on chromosome 2 in the intronic region of THSD7B \( (P = 10^{-5.17}) \); rs2691079, on chromosome 3 in the intergenic region of GBE1/LOC100289598 \( (P = 10^{-5.15}) \); and rs6758592, on...
Table 2. Single nucleotide polymorphisms associated with occurrence of interstitial lung disease

| Odds ratio | −Log₁₀P | Name                | Chromosome | Gene symbol | Gene description                                               | Gene location |
|------------|---------|---------------------|------------|-------------|-----------------------------------------------------------------|---------------|
| 4.32       | 7.93    | rs6578890           | 11         | PPFIBP2     | PPFIA binding protein 2                                         | Intron        |
| 4.07       | 5.42    | rs9804373           | 10         | RPA2P2/LOC105378390 | Replication protein A2 pseudogene 2/uncharacterized LOC105378390 | Intergenic    |
| 2.99       | 5.41    | rs9320420           | 6          | LOCI00287612/MARCKS | Uncharacterized LOCI00287612/myristoylated alanine-rich protein kinase C substrate | Intergenic    |
| 2.85       | 5.17    | rs2116538           | 2          | THSD7B      | Thrombospondin type 1 domain containing 7B                     | Intron        |
| 3.39       | 5.15    | rs2691079           | 3          | GBE1/LOC100289598 | 1,4-alpha-glucan branching enzyme 1/uncharacterized LOC100289598 | Intergenic    |
| 0.32       | 5.05    | rs6758592           | 2          | EPAS1       | Endothelial PAS domain protein 1                               | Intron        |
| 2.54       | 4.99    | rs11241716          | 5          | KRT18P16/LINCO1170 | Keratin 18 pseudogene 16/long intergenic non-protein coding RNA1170 | Intergenic    |
| 6.34       | 4.91    | rs12063103          | 1          | HIST3H2BB/RNF187 | Histone cluster 3, H2bb/ring finger protein 187               | Intron        |
| 6.34       | 4.91    | rs12084511          | 1          | RNF187/LOC100129094 | Ring finger protein 187/uncharacterized LOC100129094         | Intergenic    |
| 2.63       | 4.81    | rs1852598           | 5          | HCN1        | Hyperpolarization activated cyclic nucleotide gated potassium channel 1 | Intron        |
| 3.57       | 4.78    | rs2012393           | 7          | MAGI2       | Membrane associated guanylate kinase, WW and PDZ domain containing 2 | Intron        |
| 3.54       | 4.77    | rs7176074           | 15         | REC114      | REC114 meiotic recombination protein                           | Intron        |
| 3.12       | 4.59    | rs1375086           | 3          | GBE1        | 1,4-alpha-glucan branching enzyme 1                            | Intron        |
| 2.41       | 4.52    | rs12408079          | 1          | LOC643355/CTTNBP2NL | Uncharacterized LOC643355/CTTNBP2 N-terminal like           | Intron        |
| 10.47      | 4.44    | rs2194829           | 12         | LINCO2367   | Long intergenic non-protein coding RNA 2367                   | Intron        |

Single nucleotide polymorphisms associated with interstitial lung disease (ILD) occurrence are shown. The frequency of major allelic combinations was compared in ILD and non-ILD patients using Fisher's exact test. Bonferroni’s correction was used for multiple comparisons. The odds ratios and P-values (−log₁₀P) of the frequency of major allelic combinations between ILD and non-ILD patients are shown. The chromosome number and the gene symbols, characteristics and location were compared and are also shown.
chromosome 2 in the intronic region of EPAS1 \((P = 10^{-0.05})\). The odds ratios of the frequency of major allelic combinations between ILD and non-ILD samples is demonstrated in Table 2. The MUC5B promoter variant rs35705950 was not significantly correlated with ILD occurrence (Table 2). We also compared the frequency of major allelic combinations between UIP or NSIP and non-ILD patients and found no significant association between genetic variants in these groups.

**Discussion**

The lifetime risk of ILD in RA patients is \(\approx 8\%\), compared with 1% in the general population [23]. Several risk factors for ILD occurrence have been reported, including smoking, male gender, older age, and high RF and anti-CCP antibody titres [24]. We demonstrated significant differences in average age \((P = 0.004)\) and gender \((P < 0.001)\) between the ILD and non-ILD groups, and our findings pertaining to these clinical features are comparable to those reported previously. In addition, we showed that the expression levels of RF, anti-CCP antibodies and KL-6 were higher in the ILD group, which is consistent with the results of previous studies [24, 25].

The present study is the first to reveal a significant genome-wide association between rs6578890, an intronic SNP in PPFIBP2 located on chromosome 11, and ILD occurrence in Japanese RA patients. The protein tyrosine phosphatase receptor type-F polypeptide-interacting protein-binding protein 2, encoded by PPFIBP2, belongs to the leukocyte common antigen-related (LAR) protein tyrosine phosphatase-interacting protein (liprin) family [26]. The encoded protein, liprin beta-2, plays a role in axon guidance and neuronal synapse development by recruiting LAR protein tyrosine phosphatase to the plasma membrane [26]. Liprin beta-2 inhibits breast cancer cell migration through ERK2 signalling [27], and an increased level of mutation in PPFIBP2 has been reported in fatal cases of prostate cancer [28]. Regarding ILD occurrence, chronic damage of the alveolar epithelium triggers a series of events leading to aberrant tissue repair and destruction of the alveolar structure [29]. The subsequent wound-healing process is driven by a variety of pathogenic events, which have been described in other degenerative diseases and cancer [8]. Further investigation is required to elucidate the function of rs6578890 in aberrant tissue repair and destruction of the alveolar structure in ILD.

Another possible association between rs6578890 SNPs and ILD occurrence should be considered. Figure 2 shows the locus of rs6578890 in PPFIBP2 that is distal to cytochrome b5 reductase 2 (CYB5R2) on chromosome 11. A previous study reported that the SNPs that influence gene expression levels are called expression quantitative trait loci [30]. Chromatin regions, including expression quantitative trait loci, undergo folding to increase their proximity to the genes they regulate, and the folded module affects the expression levels of distant genes via chromatin–chromatin interactions in several diseases, including neurodegenerative diseases [31]. Thus, chromatin, including expression quantitative trait loci, can be folded, and the SNPs modify the expression level of distant genes. In our study, rs6578890 is located distal to CYB5R2 and can potentially regulate the expression of this gene. Several studies have reported an association between cytochrome members and ILD occurrence [32, 33]. Further experiments are required to elucidate the function of rs6578890 in altering CYB5R2 expression in ILD patients.

**Figure 2.** Gene map. The locus of rs6578890 in PPFIBP2 is shown on the gene map from the list of single nucleotide polymorphisms obtained from the NCBI database. rs6578890 is an intronic single nucleotide polymorphisms in PPFIBP2, located on chromosome 11 and distal to CYB5R2.
The present study has a few limitations. First, we did not perform in vitro and in vivo experiments. Second, the effect of the identified genetic variants on ILD occurrence was not investigated; additional functional analyses are required to elucidate fully the effect of these and other SNPs on the occurrence of ILD. Third, our study comprised a small cohort of patients from one region; therefore, our results might be subject to geographical bias. Further studies with a larger, more diverse patient population should be performed to confirm the observed association.

In conclusion, rs6578890, an intronic SNP located in PPFIBP2, might be associated with ILD occurrence in Japanese patients with RA. Currently, the identification of PPFIBP2 as a genetic predictor of ILD in RA patients can help to determine the risk of ILD occurrence before RA treatment is administered. Understanding the full effect of rs6578890 on the occurrence of RA-ILD will await future studies.

Data availability statement
The datasets generated and/or analysed during the present study are not publicly available due to the patent in Japan (patent number 4869834, registration date 25 November 2011) but are available from the corresponding author on reasonable request.

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