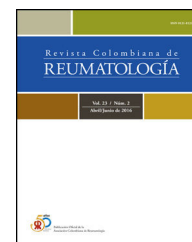




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Special article

Genetics of autoimmune-associated interstitial lung diseases: A focus on rheumatoid arthritis

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ARTICLE INFO

Article history:

Received 13 June 2023

Accepted 18 December 2023

Keywords:

Rheumatoid arthritis

Interstitial lung disease

MUC5B

Palabras clave:

Artritis reumatoide

Enfermedad pulmonar intersticial

MUC5B

ABSTRACT

Recent advances in deciphering the genetic architecture of RA-ILD support the hypothesis of RA-ILD as a complex disease with a heterogeneous phenotype encompassing at least the usual interstitial pneumonia (UIP) and non-UIP high-resolution CT patterns. The results of genetic studies support the hypothesis of a common genetic background between idiopathic pulmonary fibrosis (IPF) and RA-ILD, and more specifically RA-UIP, a subset of the disease associated with a poor prognosis. Overall, these findings suggest the existence of shared pathogenic pathways between IPF and RA-ILD providing new opportunities for future intervention in RA-ILD, particularly with drugs that have been shown to be active in IPF.

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Genética de las enfermedades pulmonares intersticiales autoinmunes asociadas: un enfoque sobre la artritis reumatoide

RESUMEN

Los recientes avances en el desciframiento de la arquitectura genética de la artritis reumatoide asociada a enfermedad pulmonar intersticial (EPI-AR) apoyan la hipótesis de que la EPI-AR es una enfermedad compleja, con un fenotipo heterogéneo, que abarca al menos los patrones de neumonía intersticial habitual (NIU) y de TC de alta resolución no NIU. Los resultados de los estudios genéticos apoyan la hipótesis de un trasfondo genético común entre la fibrosis pulmonar idiopática (FPI) y la EPI-AR, y más concretamente la NIU-AR, un subconjunto de la enfermedad asociado a un mal pronóstico. En conjunto, estos hallazgos sugieren la existencia

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de vías patogénicas compartidas entre la FPI y la EPI-AR que proporcionan nuevas oportunidades para futuras intervenciones en la EPI-AR, particularmente con fármacos que han demostrado ser activos en la FPI.

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Epidemiology

Rheumatoid arthritis (RA) is a destructive, systemic inflammatory and autoimmune disorder that affects up to 1% of the general adult population worldwide. Extra-articular disease occurs in nearly 50% of all patients with RA the lung being frequently involved.¹ Both exact prevalence and incidence of interstitial lung disease (ILD) in rheumatoid arthritis (RA) are unknown. The reported prevalence of ILD in patients with RA varies widely depending on the population studied, the method of detection and the criteria used to define ILD. Indeed, the frequency of RA-ILD disease has long been underestimated as it can remain asymptomatic for a long time and as low-sensitivity detection tools such as chest radiography still frequently used. In addition, (i) data on the natural history of RA-ILD are limited, with no currently established guidelines for screening² and (ii) several parameters that could impact the risk of occurrence of RA-ILD, such as age at RA onset, RA duration, RA disease activity, occupational exposure or smoking status vary from one study to another, making it difficult to interpret the epidemiological data of RA-ILD.

If the reported incidence of ILD among patients with RA varies considerably, it should be noted that while the incidence of extra-articular manifestations of RA appears to be decreasing, probably due to the recommendations for the management of RA including early detection, tight control and treat-to-target strategy, the estimates of incidence of RA-ILD appears to be stable or even increasing in the largest studies.³⁻⁶ In line with this, a recent analysis of a US health insurance database found an incidence of RA-ILD of 2.7 cases per 100 000 people in 2007 increasing to 3.8 in 2014.⁷ This apparent increase in the incidence of RA-ILD probably illustrates the more frequent use of more sensitive detection tools such as high-resolution chest computed tomography (HRCT) which is considered as the gold standard for radiologic assessment of ILD.⁸

A recent meta-analysis including 18 884 patients with RA found a pooled prevalence of clinically significant (i.e. symptomatic) ILD of 11%, 95%CI (7–15%).⁹ A systematic assessment of ILD by HRCT has contributed to an increase in the prevalence of RA-ILD. Indeed, it is estimated that asymptomatic ILD may complicate up to 41% of patients with RA.¹⁰ However, more recent large prospective or cross-sectional studies using HRCT and/or pulmonary function tests as a screening tool suggest that the prevalence of asymptomatic RA-ILD is around 20%.¹¹⁻¹³ This prevalence is likely to be underestimated, as in an international survey of 354 rheumatologists conducted in 2019, 44% did not consider screening for RA-ILD in patients with risk factors.¹⁴

Known genetic architecture of RA-ILD

RA-ILD is a complex disease

RA is a complex disease implicating environmental, genetic, and stochastic factors. However, the weight of genetics is underlined by family studies, estimating that more than 50% of the variance in disease risk is explained by genetic factors.¹⁵ Although the physiopathology of RA-ILD is poorly understood, this severe extraarticular manifestation of RA should be considered as a multifactorial disease involving both genetic and environmental factors.

Similarities between RA-ILD and idiopathic pulmonary fibrosis

Usual interstitial pneumonia (UIP) is a pattern of pulmonary fibrosis detected radiologically by HRCT or pathologically by lung biopsy.¹⁶ When UIP occurs in patients with an unknown cause (i.e. idiopathic UIP), it is classified as idiopathic pulmonary fibrosis (IPF), which is a chronic, progressive, and fatal disease of the lungs. When UIP occurs in patients with RA, it is known as RA-UIP, a specific subtype of RA-ILD. Compared with other autoimmune diseases, the specificity of RA-ILD lies in the relatively high proportion of patients with a HRCT UIP pattern. A recent meta-analysis including 4987 patients with RA-ILD found a pooled prevalence of UIP of 46%, whereas the other autoimmune diseases where frequently associated with a pattern of non-specific interstitial pneumonia (NSIP).⁹ RA-UIP and IPF share several features such as older age at onset (around the 6th and 7th decade, respectively), a male sex predominance, a very severe prognosis and indistinguishable patterns of ILD on HRCT (e.g. UIP).¹⁷⁻²²

RA is an autoimmune disease characterized by specific autoantibodies such as anti-citrullinated peptide antibodies (ACPAs).²³ In a community-dwelling study looking at U.S. adults enrolled in the Multi-Ethnic Study of Atherosclerosis, RA-related autoimmunity was associated with both quantitative and qualitative asymptomatic ILD notably among ever smokers.²⁴ More recently, ACPAs have been identified in patients with IPF.²⁵ Positivity for IgA-ACPA was increased in two IPF cohorts compared with general population control individuals (21.3% and 24.8% vs 5.6%). Patients with IPF were more likely to be IgA-ACPA-positive than IgG-ACPA-positive (23.2% vs 8.3%).²⁵

Based on these findings, we can hypothesize that RA-ILD (and more specifically RA-UIP) shares) genetic susceptibility factors with IPF (Fig. 1).

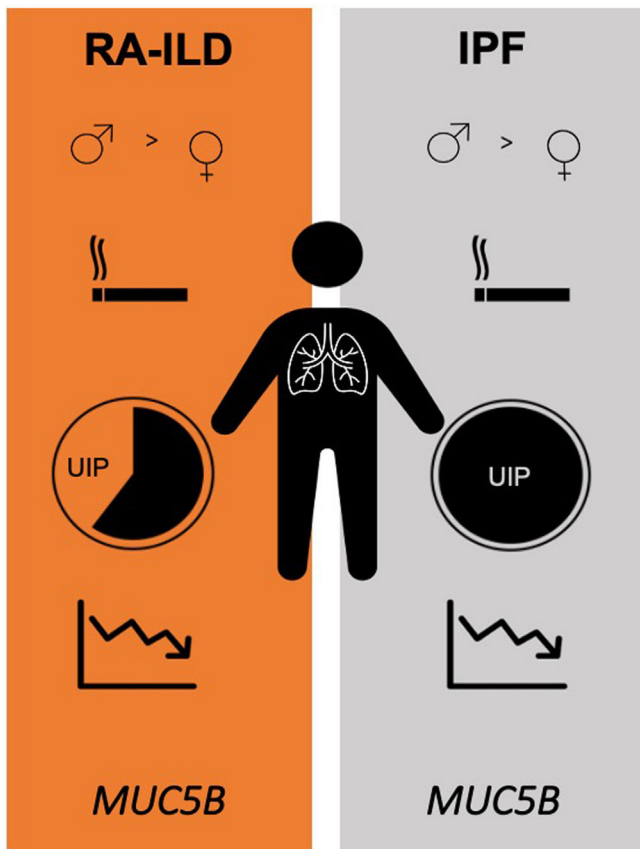


Fig. 1 – Similarities between idiopathic pulmonary fibrosis and rheumatoid arthritis associated interstitial lung disease. RA-ILD: rheumatoid arthritis associated interstitial lung disease; IPF: idiopathic pulmonary fibrosis.

Exonic rare variants

Following the hypothesis of a common genetic background between IPF and RA-ILD, a case control genetic association study investigated exonic rare variants in genes previously linked to familial pulmonary fibrosis (FPF).²⁶ Among the patients with 101 RA-ILD included, 12 (11.9%) had 13 WES-identified heterozygous mutations in the *TERT*, *RTEL1*, *PARN* or *SFTPC* coding regions. The burden test, based on 81 patients with RA-ILD and 1010 controls of European ancestry, revealed an excess of *TERT*, *RTEL1*, *PARN* or *SFTPC* rare variants in patients with RA-ILD (OR = 3.17, 95% CI (1.53–6.12); $P = 9.45 \times 10^{-2}$).²⁶ Telomeres were shorter in patients with RA-ILD carrying at least one *TERT*, *RTEL1* or *PARN* rare variant than in controls ($P = 2.87 \times 10^{-2}$). These findings support the probable contribution of FPF-linked genes to RA-ILD susceptibility. However, the study design (i.e. patients with RA-ILD vs unaffected individuals) did not allow to distinguish if the excess of FPF-linked genes exonic rare variants contributes to the risk of ILD in patients with RA or to the risk of overall RA. This last question implies that a genetic association study should be performed by comparing patients with RA-ILD and patients with RA-noILD.

Common variants

MUC5B rs35705950

The gain-of-function promoter variant rs35705950²⁷ (G>T) of the gene encoding mucin 5B (*MUC5B*) is the strongest genetic risk factor for IPF, observed in at least 50% of the patients with IPF and accounting for near 30% of the overall risk of developing this disease.^{28–36} The *MUC5B* promoter variant is associated with increased expression of *MUC5B* in lung parenchyma of unaffected controls and cases of IPF.^{27,28} Following the similarities between RA-ILD and IPF and the possibility of a common genetic background, the *MUC5B* promoter variant rs35705950 was tested for association with RA-ILD.

To test this hypothesis, a multi-ethnic association study of was performed in a large population.³⁷ Using a discovery population and multi-ethnic validation case series, the association of *MUC5B* rs35705950 was tested in 620 patients with RA-ILD, 614 patients with RA and without ILD, and 5448 unaffected controls. The derivation population revealed an association of the *MUC5B* promoter variant minor allele with RA-ILD when compared to unaffected controls (OR = 3.8 95%CI (2.8–5.2); $P = 9.7 \times 10^{-17}$). Similar to the derivation population, the *MUC5B* promoter variant was significantly over-represented among the patients with RA-ILD in the multi-ethnic validation population when compared to unaffected controls (OR = 5.5 95%CI (4.2–7.2); $P = 4.7 \times 10^{-35}$), and when the derivation and validation populations were combined (OR = 4.7 95%CI (3.9–5.8); $P = 1.3 \times 10^{-49}$). Additionally, the *MUC5B* rs35705950 T risk allele was found to increase the risk of ILD among patients with RA (OR = 3.1 95%CI (1.8–5.4); $P = 7.4 \times 10^{-5}$). Of interest and concordant with the *a priori* hypothesis of a shared genetic background between RA-UIP and IPF, the association of the *MUC5B* promoter variant with RA-ILD was restricted to the subset of patients with RA-UIP with a signal association of similar magnitude and direction to that previously reported in IPF: OR = 6.1 95%CI (2.9–13.1); $P = 2.5 \times 10^{-6}$.

Additional exploratory analyses found that other IPF risk variants (*TOLLIP* rs5743890 and *IVD* rs2034650) were also preliminarily associated with RA-ILD. The association between *MUC5B* rs35705950 and RA-ILD was independently replicated in the Finnish population. In this study, the authors estimated the lifetime risk of developing RA-ILD with respect to the *MUC5B* promoter variant. In patients with RA, *MUC5B* was found as a strong risk factor of ILD with a HR of 2.27 95%CI (1.75–2.95).³⁸ Even if the minor allele frequency of *MUC5B* rs35705950 is very low in the Asian population, the association was also replicated with RA-UIP (OR = 3.5 95%CI (1.2–10.4); $P = 0.023$).³⁹ Interestingly, the *MUC5B* rs35705950 variant has not been associated with systemic sclerosis-related ILD (SSc-ILD)³² nor antisynthetase syndrome,⁴⁰ two diseases in which the predominant pattern is NSIP. Conversely, *MUC5B* rs35705950 contributes to the risk of asbestosis and myeloperoxidase-antineutrophil cytoplasmic antibody-associated vasculitis-related ILD, two diseases in which, like for RA-ILD, the UIP pattern is prevalent.^{41,42} These findings suggest that the *MUC5B* rs35705950 variant may prove to be a generalized risk factor for UIP, and not simply limited to IPF and RA-UIP.

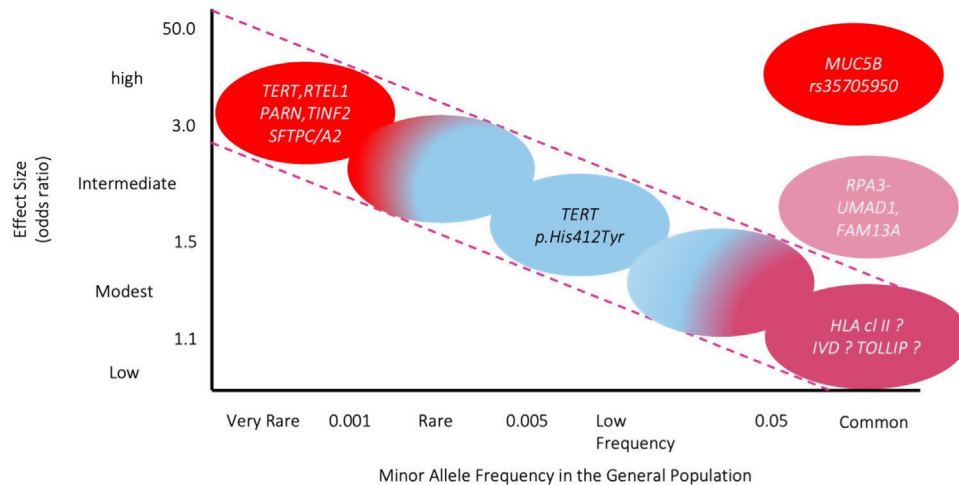


Fig. 2 – Genetic architecture of rheumatoid arthritis associated interstitial lung disease.

Additional common variants of potential interest

Recently, a genome-wide association study performed in the Japanese population that included 358 patients with RA-ILD and 4550 patients with RA without ILD (RA-noILD) identified the RPA3-UMAD1 rs12702634 single nucleotide polymorphism (SNP) as a new RA-ILD risk variant (OR = 2.04 95%CI (1.59–2.60); $P = 1.5 \times 10^{-8}$).⁴³ Sub-analysis according to chest HRCT pattern found a stronger association in patients with RA-ILD having a UIP and probable UIP patterns: OR = 1.86 95%CI (0.97–3.58); $P = 0.062$ and OR = 2.26 95%CI (1.36–3.73); $P = 0.0015$, respectively. The RPA3-UMAD1 rs12702634 SNP is located in the intronic region of RPA3 and UMAD1 within an enhancer possibly involved in the modulation of gene expression in immune cells.⁴³ This association was not replicated in an independent Japanese population.⁴⁴ To date, the contribution of RPA3-UMAD1 rs12702634 to the genetic architecture of RA-ILD in non-Asian populations remains to be determined.

A recent GWAS, performed in a relatively small population (i.e. 60 patients with RA-ILD compared to 1058 patients with RA-noILD) and without a replication step found the association between MUC5B rs35705950 and RA-ILD and suggested that 3 additional known IPF-risk variants (TOLLIP rs111521887, FAM13A rs2609255 and TERT rs2736100) contributed to the risk of ILD in European RA.⁴⁵ A case-control association study investigating FAM13A rs2609255 in the Japanese RA population (208 patients with RA-ILD vs 420 patients with RA-noILD) found a significant contribution of FAM13A rs2609255 to the risk of RA-ILD (OR = 1.53, 95% CI (1.12–2.11); $P = 0.0092$). FAM13A rs2609255 was significantly associated with RA-UIP in male patients (OR 3.65, 95% CI 1.52–8.73; $P = 0.0043$) under a recessive model.⁴⁶

Lastly, a case-control genetic association study of a Japanese population, not including a replication step, found an association between HLA-DRB1*1502 and RA-ILD.⁴⁷ A recent intra-case genome-wide association study performed in the same population and comparing patient with RA with and without ILD did not find a significant association between RA-ILD and the HLA-DRB1 locus.⁴³ Therefore, the exact role of the HLA-DRB1 locus to the RA-ILD susceptibility remains to be elucidated.

The current state of knowledge on the genetic architecture of RA-ILD is represented in Fig. 2.

Finally, the genetic background of RA-ILD probably differs from that of other autoimmune diseases-related ILD. For example, the main genetic risk factors for SSc-ILD involve variants located in genes encoding actors of the type 1 interferon pathway and, more broadly, in innate and adaptive immunity⁴⁸ which do not appear to contribute to the risk of RA-ILD in the two GWAS studies reported.

Genetic risk factors and screening for RA-ILD

The relatively high prevalence of asymptomatic ILD seen on chest HRCT scan in patients with RA shows that a detection based on only respiratory symptoms is not relevant. symptomatic, RA-ILD should be assessed by chest HRCT scan allowing for (1) the diagnosis of ILD and (2) both qualitative (HRCT patterns) and quantitative (extent) assessment of ILD.^{49–52} Consequently, the challenge of RA-ILD screening arises only in the context of the absence of respiratory symptoms in selected patients with RA at particularly high-risk of ILD.^{49,53} Recently developed therapeutic interventions could help reduce the decline of lung function in patients with a progressive condition.⁵⁴ Early identification of ILD in patients with RA may inform our understanding of disease pathogenesis and may provide a therapeutic window of opportunity to prevent progression to symptomatic RA-ILD. The identification of high-risk RA with RA who may benefit from HRCT screening at an early and asymptomatic stage of the disease is an important unmet need in RA-ILD.⁵⁵

To date only 2 studies aimed to identify independent risk factors (including genetic factors) for asymptomatic ILD in patients with RA. The first is a prospective study involving 184 patients with RA without known ILD. All the individuals had lung imaging performed with HRCT scans and were genotyped for MUC5B rs35705950. In this population, the majority were RF and anti-CCP positive with a median RA duration of 8.5 years and the prevalence of asymptomatic ILD was 21%. Multiple logistic regression models found MUC5B rs35705950 as an

independent risk factor for asymptomatic RA-ILD.¹¹ The second study, included a derivation and a replication population constituted of patients without pulmonary symptoms from 2 prospective RA cohorts who underwent chest HRCT scans. All patients were genotyped for *MUC5B* rs35705950. Derivation and replication populations included 163 and 89 patients with RA, respectively. The prevalence of asymptomatic RA-ILD was 19.0% and 16.9%, respectively. Briefly, independent risk factors for asymptomatic RA-ILD were the *MUC5B* rs35705950 T risk allele (odds ratio (OR) = 3.74; 95% CI (1.37–10.39), male sex, older age at RA onset and increased mean DAS28-ESR. A derived risk score was developed and validated in the replication cohort. Excluding *MUC5B* rs35705950 from the model provided a lower goodness of fit supporting its important contribution to asymptomatic RA-ILD risk. All these findings could help clinicians in their daily practice and more extensively for future recommendations in RA-ILD screening.

Conclusion

RA-ILD is a multifactorial disease whose determinism involves environmental and genetic factors. Over the last decade, there has been growing interest in identifying phenotypic markers of RA associated with RA-ILD. It is only very recently that we have become interested in understanding the genetic architecture of the disease. To date, *MUC5B* rs35705950 remains the main genetic risk factor which seems likely to be of interest for screening for the disease.

Future genome-wide association studies are needed to establish the genetic background of RA-ILD. It should be noted that this genetic background will probably be distinct for each specific subset of the disease. Indeed, RA-ILD is incorrectly considered to be a single entity, whereas it is formally heterogeneous, as illustrated by the variability of the HRCT patterns. One illustration of this distinct genetic background would be the exclusive association of *MUC5B* rs35705950 with RA-UIP.

Finally, an effort should be made to identify future prognostic factors for RA-ILD, including the potential role of specific genetic variants. International collaborative efforts are needed to address these issues.

Conflict of interests

The authors declare that they have no conflict of interest.

Appendix A. Supplementary material

The Spanish translation of this article is available as supplementary material at doi:[10.1016/j.rcreu.2023.12.002](https://doi.org/10.1016/j.rcreu.2023.12.002).

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