

# Towards clinical significance of the *MUC5B* promoter variant and risk of rheumatoid arthritis-associated interstitial lung disease

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While rheumatoid arthritis-associated interstitial lung disease (RA-ILD) has been known to be a serious extra-articular rheumatoid arthritis (RA) manifestation for decades, RA-ILD and other pulmonary sequelae of RA have been of intense interest in recent years. Patients with RA have excess respiratory mortality of RA compared with the general population.<sup>1,2</sup> This respiratory burden of RA seems to be specific for patients with seropositive RA,<sup>1</sup> and RA-ILD is likely a key contributor to the respiratory burden of RA. Median survival after clinical RA-ILD detection is poor, ranging from 3 years to 8 years in previous studies.<sup>3-5</sup> Unlike nearly all other outcomes in RA, prevalence of RA-ILD does not seem to be decreasing over calendar time.<sup>5</sup> This may be explained by several factors that include increased longevity of patients, improved articular disease activity unmasking symptoms of dyspnoea on exertion, increased awareness by clinicians of RA-ILD, greater ease in obtaining advanced chest imaging, or perhaps by medications used to treat RA-ILD. Thus, RA-ILD is a serious public health condition for patients with RA. Establishing the risk and identifying risk factors for RA-ILD are therefore of utmost importance. In *Annals of the Rheumatic Diseases*, Palomäki and colleagues investigate the lifetime risk of RA-ILD related to the *MUC5B* promoter variant.<sup>6</sup>

RA-ILD is a heterogeneous condition that is notoriously difficult to diagnose. Usual interstitial pneumonia (UIP) is the most common RA-ILD, considered to be fibrotic and progressive. A recent meta-analysis found that the UIP subtype had worse prognosis compared with other

RA-ILD subtypes.<sup>7</sup> Idiopathic pulmonary fibrosis (IPF) shares many of the same clinical and imaging features of UIP in RA-ILD. A common promoter variant of *MUC5B* (G>T at the rs35705950 single-nucleotide polymorphism) was identified as an important genetic risk factor for IPF.<sup>8</sup> Subsequently, the *MUC5B* promoter variant was associated with overall RA-ILD risk, specifically the UIP subtype, compared with patients with RA without ILD as well as general population controls.<sup>9</sup> However, in that previous study, there was no association of the *MUC5B* promoter variant with RA risk or serostatus, and there was no gene-smoking interaction for RA-ILD risk.<sup>9</sup>

People with the *MUC5B* promoter variant produce higher quantities of mucin 5B in lung parenchyma and airways.<sup>10</sup> While the exact mechanisms linking the *MUC5B* promoter variant with IPF and UIP risk are still being elucidated, the relative overabundance of the mucin 5B protein may lead to local recruitment of immune cells that eventually leads to long-term damage and fibrosis that presents clinically as fibrotic lung disease. The parallels between IPF and UIP have led some to speculate that these may be the same entity, the latter in a patient that just happens to also have RA. However, the prevalence of UIP is generally reported to be higher than would be expected by chance alone, considering the independent prevalence of IPF and RA. Previous studies have also identified RA-specific characteristics, such as RA-related autoantibodies and articular disease activity, as risk factors for RA-ILD.<sup>11-14</sup> Thus, there may be a synergistic relationship between the *MUC5B* promoter variant and RA for RA-ILD risk. Other established RA-ILD risk factors include older age at RA onset, male sex, cigarette smoking and longer RA duration, among others.<sup>13</sup>

Palomäki and colleagues used FinnGen to study the relationship of the *MUC5B* promoter variant with the lifetime risk of RA-ILD.<sup>6</sup> FinnGen was assembled

from other prospective studies and linked to nationwide registers in Finland to link genetic and clinical data with up to 50 years of follow-up. They analysed 293 972 individuals to determine presence and dates of RA and ILD, identified using medication reimbursement codes and diagnoses from hospital inpatient and outpatient registries.<sup>6</sup> They then stratified by presence or absence of the *MUC5B* promoter variant and also performed separate analyses among men and women. In the entire population, about 20% had at least one copy of the *MUC5B* promoter variant.<sup>6</sup> Overall, the estimated risk of ILD was 1.5% by 80 years of age (considered as a surrogate for lifetime risk). Within RA, the lifetime risk of RA-ILD was higher, at 6.1%.<sup>6</sup> Presence of the *MUC5B* promoter variant was strongly associated with ILD risk within RA compared with absence of the variant (HR 2.27, 95% CI 1.75 to 2.95).<sup>6</sup> The lifetime risk of ILD in RA for those with the *MUC5B* promoter variant was 16.8% (compared with 4.4% in the general population) and seemed to specifically emerge after age of 65 years.<sup>6</sup> Consistent with other studies, men with RA had a higher lifetime risk of ILD than women with RA. However, the lifetime risk for RA-ILD among those with the *MUC5B* promoter variant was quite high for both men (20.9%) and women (14.5%).<sup>6</sup> Considering that the *MUC5B* promoter variant is relatively common, this means that many patients with RA may be harbouring this genetic variation that could dramatically alter their lifetime risk for RA-ILD.

Beyond risk for RA-ILD, there was also some evidence that the *MUC5B* promoter variant could also impact overall RA risk.<sup>6</sup> Those with the variant had slightly increased risk for RA in FinnGen, which was also replicated in the UK Biobank. The relationship persisted when eliminating patients from the analysis who developed ILD prior to RA. A possible mechanism for this observation could be that the *MUC5B* promoter variant could impact RA-related autoantibody production, perhaps by leading to pulmonary mucosal inflammation and immune tolerance loss prior to articular RA onset. However, large genetic studies have not identified a relationship of *MUC5B* with overall or seropositive RA risk,<sup>6</sup> so these findings should be considered preliminary.

Some limitations need to be considered. Most notably, cigarette smoking was not measured and so could not be considered in the analysis. Smoking likely mediates the relationships between *MUC5B*, RA, and RA-ILD. It would be

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of clinical and public health importance to determine how smoking may modify the RA-ILD risks observed in this study, particularly among patients with the *MUC5B* promoter variant. Likewise, RA-related autoantibody levels, disease activity, medications and severity likely impact RA-ILD risk<sup>13</sup> and were unable to be incorporated in analyses. The past and current RA disease states would need to be considered for clinical application of the *MUC5B* promoter variant. The authors did not consider patients with two copies of the promoter variant who are likely at even higher risk of RA-ILD. As already noted, RA-ILD is a heterogeneous phenotype and the *MUC5B* promoter variant is only expected to strongly impact UIP risk within RA. Identifying RA-ILD in administrative datasets and institutional biobanks may be inaccurate<sup>15</sup> and could have at least slightly overestimated its incidence in this study.<sup>6</sup> The results emphasise how much more common RA-ILD is compared with the general population, again suggesting that RA-ILD is a distinct entity and not IPF in a patient who happens to have RA. However, without data on the UIP subtype, this is not yet definitive.

While lifetime risk of ILD is an important clinical metric to consider, these findings suggest relatively little impact of the variant until patients have reached the age of 60 years. Even then, this would be predictive of RA-ILD within 20 years, a relatively long window to monitor patients for signs and symptoms. If this genetic variant was measured many years before this 'risk window of RA-ILD', it may invoke either decades of anxiety or a false sense of reassurance if RA-ILD does not immediately develop when checked. As also noted in other studies, RA-ILD risk seems to be most pronounced in older patients.<sup>16,17</sup> More research is needed to understand how *MUC5B* and the ageing process may impact RA-ILD risk.<sup>18</sup>

In conclusion, the *MUC5B* promoter variant has clearly emerged as the single most important genetic risk factor for RA-ILD. This is evidenced by one in every six patients with RA with this variant developing RA-ILD by age of 80 years in this study. As such, any model of RA-ILD pathogenesis, particularly UIP, needs to incorporate the variant into its framework, analogous to the *HLA-DRB1* shared epitope in RA pathogenesis and *HLA-B27* in spondyloarthritis pathogenesis. While these findings have clear research importance for the field of RA-ILD, clinical application is not yet determined. This

would require a clear determination on who to order the test, the diagnostic and prognostic implications, and actions to mitigate risk. This study suggests an age window and provides prognostic implications on which testing the *MUC5B* promoter variant may be considered as appropriate. Further studies are needed to determine actions such as smoking cessation or pharmacological therapies, such as anti-inflammatories or antifibrotics, that could possibly alter the natural history of RA-ILD.

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