UNIVERSITY OF HELSINKI

https://helda.helsinki.fi

Lifetime risk of rheumatoid arthritis-associated interstitial lung disease in MUC5B mutation carriers

FinnGen Rheumatology Clinical Expe; Palomaki, Antti; Palotie, Aarno; Koskela, Jukka; Eklund, Kari K. ...

2021-12
Elsevier B.V.
http://hdl.handle.net/10138/337522
FinnGen Rheumatology Clinical Expe, Palomaki, A, Palotie, A, Koskela, J, Eklund, K K, Pirinen, M, Ripatti, S, Laitinen, T, Mars, N & Kerola, A M 2021, 'Lifetime risk of rheumatoid arthritis-associated interstitial lung disease in MUC5B mutation carriers', Annals of the Rheumatic Diseases, vol. 80, no. 12, 125011, pp. 1530–1536. https://doi.org/10.1136/annrheumdis-2021-220698

Downloaded from Helda, University of Helsinki institutional repository. https://helda.helsinki.fi
This is an electronic reprint of the original article.
This reprint may differ from the original in pagination and typographic detail.
Please cite the original version.

OPEN ACCESS

CLINICAL SCIENCE

Lifetime risk of rheumatoid arthritis-associated interstitial lung disease in *MUC5B* mutation carriers

Antti Palomäki ,[1,2] FinnGen Rheumatology Clinical Expert Group, Aarno Palotie,[2,3,4] Jukka Koskela,[2] Kari K Eklund,[5,6] Matti Pirinen,[2,7,8] FinnGen, Samuli Ripatti,[2,7,9] Tarja Laitinen,[10] Nina Mars [2]

Handling editor Josef S Smolen

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2021-220698).

For numbered affiliations see end of article.

Correspondence to
Dr Nina Mars, Institute for Molecular Medicine Finland (FIMM), Helsinki Institute of Life Science, University of Helsinki, Helsinki FI-00014, Finland; nina.mars@helsinki.fi

Received 1 May 2021
Accepted 20 July 2021
Published Online First 3 August 2021

ABSTRACT

Objectives To estimate lifetime risk of developing rheumatoid arthritis-associated interstitial lung disease (RA-ILD) with respect to the strongest known risk factor for pulmonary fibrosis, a *MUC5B* promoter variant.

Methods FinnGen is a collection of epidemiological cohorts and hospital biobank samples, integrating genetic data with up to 50 years of follow-up within nationwide registries in Finland. Patients with RA and ILD were identified from the Finnish national hospital discharge, medication reimbursement and cause-of-death registries. We estimated lifetime risks of ILD by age 80 with respect to the common variant rs35705950, a *MUC5B* promoter variant.

Results Out of 293 972 individuals, 1965 (0.7%) developed ILD by age 80. Among all individuals in the dataset, *MUC5B* increased the risk of ILD with a HR of 2.44 (95% CI: 2.22 to 2.68). Out of 6869 patients diagnosed with RA, 247 (3.6%) developed ILD. In patients with RA, *MUC5B* was a strong risk factor of ILD with a HR similar to the full dataset (HR: 2.27, 95% CI: 1.75 to 2.95). In patients with RA, lifetime risks of ILD were 16.8% (95% CI: 13.1% to 20.2%) for *MUC5B* carriers and 6.1% (95% CI: 5.0% to 7.2%) for *MUC5B* non-carriers. The difference between risks started to emerge at age 65, with a higher risk among men.

Conclusion Our findings provide estimates of lifetime risk of RA-ILD based on *MUC5B* mutation carrier status, demonstrating the potential of genomics for risk stratification of RA-ILD.

Key messages

What is already known about this subject?

► Interstitial lung disease (ILD) is one of the most common extra-articular complications of rheumatoid arthritis (RA). The *MUC5B* promoter variant rs35705950 is an important genetic risk factor for ILD, and case–control studies have identified it to be a risk factor also for RA-ILD.

What does this study add?

► By integrating large-scale genotype data with clinical data from nationwide healthcare registries, we show that in patients with RA, *MUC5B* variation is strongly associated with a lifetime risk of RA-ILD.

How might this impact on clinical practice or future developments?

► This study highlights the importance of genetic predisposition on the development of RA-ILD. Further studies are needed to investigate the impact of *MUC5B* on outcomes of RA-ILD.

INTRODUCTION

Interstitial lung disease (ILD) is one of the most common extra-articular manifestations of rheumatoid arthritis (RA).[1] The cumulative risk of developing clinical ILD during the RA disease course has varied in different studies, ranging from 5.0% to 7.7% in long-term follow-up studies of RA cohorts[1–3] to up to 10% in a study using death records.[4] Even higher estimates for subclinical radiographic findings consistent with ILD have been observed in patients with RA, ranging from 19% to 33%.[5–7] Although the RA-ILD course can vary, the disease is associated with significantly increased mortality compared with patients with RA without ILD.[3 4 8]

Clinical risk factors for RA-ILD include older age, male gender, tobacco smoking, high levels of anticitrullinated protein antibodies and disease activity.[2 9] The strongest known genetic risk factor for idiopathic pulmonary fibrosis (IPF) is the common variant rs35705950, a promoter variant near the *MUC5B* gene.[10] A recent case–control study has demonstrated that the *MUC5B* promoter variation is associated with an increased risk of ILD among patients with RA.[11] The aim of this study was to evaluate the lifetime risk of ILD in patients with RA, comparing the risk to the population, and estimate how the *MUC5B* promoter variant modifies these risks in the real-world setting.

METHODS

FinnGen is a collection of prospective epidemiological and disease-based cohorts, and hospital biobank samples. The unique personal identification number links the genotypes to multiple nationwide registries, and cases were identified through the national hospital discharge registry (starting from 1968) including both inpatient and outpatient data, the national death registry (1969–) and the medication reimbursement registry (1964–).

RA was defined as patients having medication reimbursement for inflammatory rheumatic diseases (code 202), with an additional requirement of two contacts with the International Classification of Diseases, Tenth Revision (ICD-10) codes

Linked

► http://dx.doi.org/10.1136/annrheumdis-2021-220856

Check for updates

© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY. Published by BMJ.

To cite: Palomäki A, , Palotie A, *et al*. *Ann Rheum Dis* 2021;**80**:1530–1536.

Ann Rheum Dis: first published as 10.1136/annrheumdis-2021-220698 on 3 August 2021. Downloaded from http://ard.bmj.com/ on December 14, 2021 at University of Helsinki. Protected by copyright.

beginning with M05 (seropositive RA) or M06 (seronegative RA). In our recent validation study of RA diagnoses in Finnish biobank patients (unpublished), this combination resulted in a positive predictive value of 0.87 compared with chart review. Negative predictive value for any RA diagnosis was 1.0. Those without RA who had other inflammatory rheumatic diseases or inflammatory bowel disease were excluded.

ILD cases were identified with J84, M05.1/J99.0 (ICD-10), 515, 516 (ICD-9) or 484.99 or 517.01 (ICD-8) with following criteria: (1) the first and only record in the death registry or (2) after the initial diagnosis, a second contact (or death due to ILD) was required within 5 years, that is, we excluded individuals with no further healthcare contacts with ILD within 5 years. No exclusions were made based on temporality of RA and ILD. For both RA and ILD, age at onset was defined as age at first registered diagnosis.

For *MUC5B* (mucin 5B, oligomeric mucus/gel-forming), we studied carriers of the minor allele for the promoter variant rs35705950 (G>T) with minor allele frequency 0.1 (no enrichment compared with non-Finnish Europeans[12]) and mean INFO 0.948 indicating high imputation quality. Individuals homozygous for the variant were analysed jointly with the heterozygotes.

Start of follow-up was set at birth, with follow-up ending at the first record of the endpoint of interest, death, or at the end of follow-up on 31 December 2019, whichever came first. Using the Cox proportional hazards model, we estimated adjusted HRs and 95% CIs (CI). With age as time scale, all regression models were stratified by sex, adjusted for 10 principal components of ancestry, FinnGen genotyping array and cohort. We report cumulative incidences with 95% CIs by age 80. We used R V.3.6.3. Detailed information on genotyping, disease definitions and analyses are provided in online supplemental methods.

Patient and public involvement

This study was carried out without direct patient and public involvement.

RESULTS

Among 293 972 individuals (mean age at the end of follow-up: 59.8, SD: 17.3, 56.4% women), we identified 1965 patients (1172 men, 793 women) diagnosed with ILD by end of follow-up. Out of 6869 patients with RA (mean age at onset: 49.4, SD: 14.9, 71.1% women), 247 (3.6%) had been diagnosed with ILD. Out of these 247 individuals, 20 (8.1%) had been diagnosed with ILD >1 year before the earliest record of RA, 36 (14.6%) within a year prior to or after the earliest record of RA and 191 (77.3%) >1 year after. Out of patients without RA, 19.3% were *MUC5B* carriers, and out of patients with RA, 20.9%. Among all individuals in the dataset, the *MUC5B* promoter variant rs35705950 was associated with ILD with a HR of 2.44 (2.22–2.68, $p=3.87\times10^{-77}$), and among patients with RA, with a HR of 2.27 (1.75–2.95, $p=8.15\times10^{-10}$). In a formal test for interaction by introducing an interaction term in the regression model, we found no evidence of an interaction between *MUC5B* and RA (p=0.16). These interaction tests indicate that the effect of *MUC5B* is similar in the population and in patients with RA.

Next, we quantified the lifetime risk of ILD for four groups: (1) *MUC5B* non-carriers in the population, (2) *MUC5B* carriers in the population, (3) *MUC5B* non-carriers with RA and (4) *MUC5B* carriers with RA (figure 1, table 1). The corresponding lifetime risks were (1) 1.5% (95% CI: 1.3% to 1.6%), (2) 4.4% (95% CI: 4.1%–4.8%), 3) 6.1% (95% CI: 5.0%–7.2%) and (4) 16.8% (95% CI: 13.1%–20.2%). In sex-specific analyses, the lifetime risk was 20.9% (95% CI: 14.1%–27.1%) in men with RA who are *MUC5B* carriers, and the corresponding lifetime risk in women was 14.5% (95% CI: 10.2%–18.6%). Accounting for competing risks (non-ILD causes of death) yielded marginally lower estimates of lifetime risks, particularly in men (online supplemental table 1).

Lastly, we observed an association between *MUC5B* and risk of RA (HR: 1.10, 1.04–1.17, p=0.0009), with a somewhat larger association in men (HR: 1.17, 1.05–1.30, p=0.005) than in women (HR: 1.08, 1.01–1.16, p=0.04). The effects remained similar when excluding all 1172 men with ILD (HR: 1.13 in men, 1.01–1.26, p=0.03) and all 793 women with ILD (HR: 1.05 in women, 0.98–1.13, p=0.19). This observation was replicated in UK Biobank (1911 RA cases; see online supplemental methods for details) with a HR of 1.15 (1.03–1.28, p=0.01). Meta-analysing the effects from FinnGen and UK Biobank, the HR was 1.11 (1.06–1.17, $p=4.07\times10^{-5}$).

DISCUSSION

In this large observational cohort study, we demonstrate that a combination of RA and *MUC5B* variation confers a 10-fold elevated risk of ILD compared with the population. Every sixth

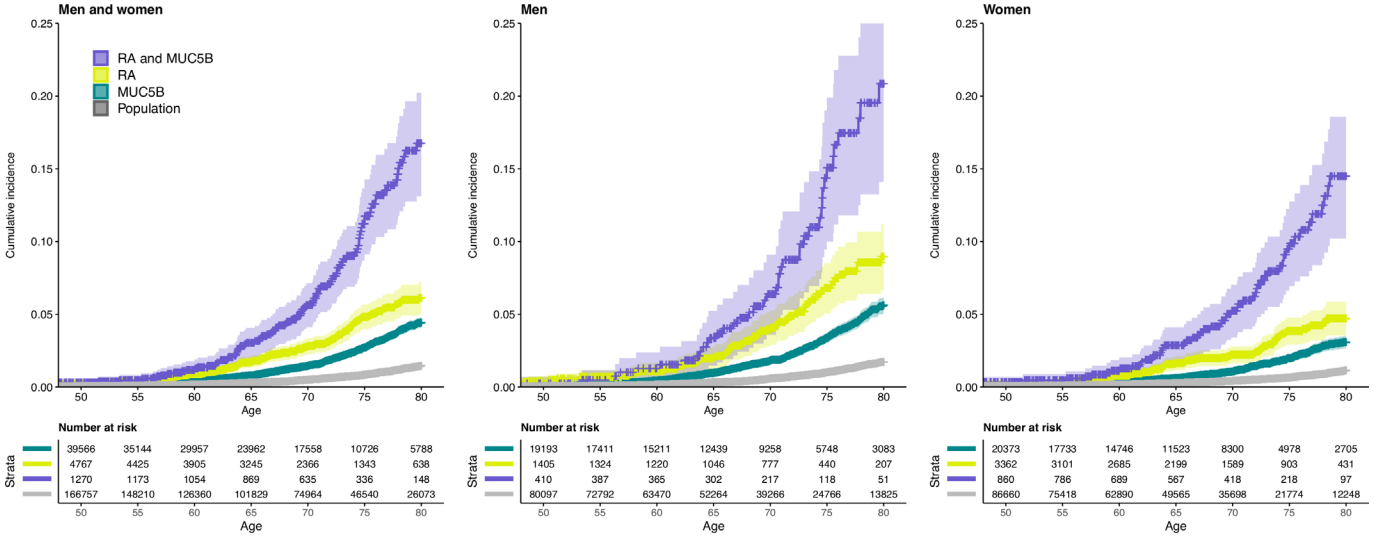


Figure 1 Lifetime risk of interstitial lung disease in the population for *MUC5B* carriers and non-carriers with respect to diagnosis of RA. The risks are shown for men and women both combined and individually. *MUC5B*=carriers of the minor allele for the promoter variant rs35705950. Sample size: 293 972 (128 233 men and 165 739 women). RA, rheumatoid arthritis.

Ann Rheum Dis: first published as 10.1136/annrheumdis-2021-220698 on 3 August 2021. Downloaded from http://ard.bmj.com/ on December 14, 2021 at University of Helsinki. Protected by copyright.

Table 1 Data characteristics, and effect of RA and *MUC5B* on risk of ILD

	Individuals without RA		Individuals with RA	
	Non-carriers of *MUC5B* promoter variant	Carriers of *MUC5B* promoter variant	Non-carriers of *MUC5B* promoter variant	Carriers of *MUC5B* promoter variant
N	231 860	55 243	5431	1438
ILD cases	1007	711	151	96
ILD cases in men/women	600/407	461/250	70/81	41/55
Age at ILD onset, men/women (mean (SD))	66.9 (10.4)/63.0 (13.3)	67.9 (8.3)/65.3 (11.1)	65.6 (9.1)/64.1 (9.2)	68.5 (7.4)/66.9 (8.7)
Risk of ILD in women and men				
Lifetime risk, % (95% CI)	1.5 (1.3–1.6)	4.4 (4.1–4.8)	6.1 (5.0–7.2)	16.8 (13.1–20.2)
HR (95% CI)	Reference	2.49 (2.25–2.75)	4.99 (4.20–5.94)	9.84 (7.96–12.2)
P value	–	1.24×10^{-71}	2.67×10^{-74}	4.40×10^{-99}
Risk of ILD in men				
Lifetime risk, % (95% CI)	1.7 (1.6–1.9)	5.6 (5.1–6.2)	9.0 (6.7–11.2)	20.9 (14.1–27.1)
HR (95% CI)	Reference	2.63 (2.31–2.98)	5.72 (4.46–7.34)	8.23 (5.96–11.4)
P value	–	2.04×10^{-50}	6.81×10^{-43}	1.56×10^{-37}
Risk of ILD in women				
Lifetime risk, % (95% CI)	1.1 (1.0–1.3)	3.1 (2.6–3.5)	4.7 (3.6–5.9)	14.5 (10.2–18.6)
HR (95% CI)	Reference	2.26 (1.92–2.66)	4.49 (3.53–5.70)	11.9 (8.96–15.8)
P value	–	1.46×10^{-22}	1.31×10^{-34}	7.86×10^{-66}

ILD, interstitial lung disease; RA, rheumatoid arthritis.

patient with RA carrying the *MUC5B* risk allele was diagnosed with ILD by age 80, and the risk rapidly increased after age 65. A case–control study by Juge and colleagues recently demonstrated enrichment of *MUC5B* carriers in patients with RA-ILD, with supporting evidence from gene expression in lung parenchyma and high-resolution imaging.[11] Using large-scale biobank data, we now show how this finding translates to lifetime risks and demonstrate the potential of genomics for risk stratification of RA-ILD and early identification of patients.

Prevalence of RA-ILD shows high variability in the literature depending on the population, diagnostic methods and disease definitions used.[13] Our lifetime risks compare well with previous estimates of clinically significant disease, reported to occur in up to 5%–10% of patients with RA.[2–4] We show that the effect of *MUC5B* is similar in the population and in patients with RA, but as both *MUC5B* and RA are important risk factors of ILD, patients with RA who are *MUC5B* carriers are at a much higher risk of ILD than *MUC5B* carriers without RA.

The common variant rs35705950 in the *MUC5B* promoter is strongly associated with upregulation of *MUC5B* expression in the lungs, and the general association between the variant and ILD has been widely replicated.[10 11 14] In addition, evidence from fine-mapping indicates that rs35705950 might be a causal variant: Bayesian fine-mapping analyses of genome-wide association study (GWAS) results can be used for defining variant sets (credible sets), that with high probability contain one or several causal variants. Several sources report rs35705950 as the only variant in the credible sets for the locus in GWASs on ILD and IPF.[15 16]

We were unable to account for some important risk factors, such as smoking and disease activity, and did not consider other common or rare genetic risk factors,[14 17] all of which are likely to further contribute to the risk. We did not have information about histological or radiological patterns of ILD. The study was limited to individuals of European ancestry, but *MUC5B* may be a relevant risk factor also in other populations[11], although many have allele frequencies that are much lower.[12] With a prevalence of 2.3% for RA and 0.7% for ILD, our sample is slightly enriched in cases, which may affect our estimates. Although ILD was identified through healthcare registries, recurring healthcare encounters were required to reduce the proportion of false positives in our study, and the long-term risk of ILD in patients with RA was in line with previous studies.[1–4] Patients with RA might be exposed to more chest imaging as part of their standard care and due to increased awareness for the risk of ILD particularly during recent years, which could overestimate the risk difference between patients with and without RA. We also observed a modest association between *MUC5B* and RA, which was replicated in UK Biobank. This association was not detected in a previous study with a smaller sample size by Juge and colleagues.[11] This tentative finding, which was clearer in men, requires further replication with consideration of other important risk factors, such as smoking. As the effects remained similar when excluding all patients with ILD, we propose that the temporal sequence of ILD and RA is unlikely to impact the association.

In conclusion, the *MUC5B* promoter variant is a common risk factor for ILD in patients with RA and confers a significantly elevated lifetime risk of ILD. This study demonstrates the potential of genomics for risk stratification of RA-ILD and highlights the importance of genetic predisposition on the development of RA-ILD. Studies are needed to further investigate the interaction of clinical and genetic risk factors in the development of RA-ILD, and the impact of *MUC5B* on outcomes of RA-ILD.

Author affiliations
[1]Centre for Rheumatology and Clinical Immunology, and Department of Medicine, Turku University Hospital and University of Turku, Turku, Finland
[2]Institute for Molecular Medicine Finland (FIMM), Helsinki Institute of Life Science, University of Helsinki, Helsinki, Finland
[3]Analytic and Translational Genetics Unit, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA
[4]Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA
[5]Department of Rheumatology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
[6]Orton Orthopaedic Hospital, Helsinki, Finland
[7]Department of Public Health, University of Helsinki, Helsinki, Finland
[8]Department of Mathematics and Statistics, University of Helsinki, Helsinki, Finland
[9]Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA

Ann Rheum Dis: first published as 10.1136/annrheumdis-2021-220698 on 3 August 2021. Downloaded from http://ard.bmj.com/ on December 14, 2021 at University of Helsinki. Protected by copyright.

[10]Administration Center, Tampere University Hospital, Tampere, Finland

Twitter Nina Mars @ninajmars

Acknowledgements The FinnGen project is funded by two grants from Business Finland (HUS 4685/31/2016 and UH 4386/31/2016) and the following industry partners: AbbVie Inc, AstraZeneca UK Ltd, Biogen MA Inc, Celgene Corporation, Celgene International II Sàrl, Genentech Inc, Merck Sharp & Dohme Corp, Pfizer Inc, GlaxoSmithKline Intellectual Property Development Ltd, Sanofi US Services Inc, Maze Therapeutics Inc, Janssen Biotech Inc and Novartis AG. Following biobanks are acknowledged for delivering biobank samples to FinnGen: Auria Biobank (www.auria.fi/biopankki), THL Biobank (www.thl.fi/biobank), Helsinki Biobank (www.helsinginbiopankki.fi), Biobank Borealis of Northern Finland (https://www.ppshp.fi/Tutkimus-ja-opetus/Biopankki/Pages/Biobank-Borealis-briefly-in-English.aspx), Finnish Clinical Biobank Tampere (www.tays.fi/en-US/Research_and_development/Finnish_Clinical_Biobank_Tampere), Biobank of Eastern Finland (www.ita-suomenbiopankki.fi/en), Central Finland Biobank (www.ksshp.fi/fi-FI/Potilaalle/Biopankki), Finnish Red Cross Blood Service Biobank (www.veripalvelu.fi/verenluovutus/biopankkitoiminta) and Terveystalo Biobank (www.terveystalo.com/fi/Yritystietoa/Terveystalo-Biopankki/Biopankki/). All Finnish Biobanks are members of BBMRI.fi infrastructure (www.bbmri.fi). Finnish Biobank Cooperative-FINBB (https://finbb.fi/) is the coordinator of BBMRI-ERIC operations in Finland.

Collaborators FinnGen Rheumatology Clinical Expert Group: Kari Eklund (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Antti Palomäki (Hospital District of Southwest Finland, Turku, Finland); Pia Isomaki (Pirkanmaa Hospital District, Tampere, Finland); Laura Pirilä (Hospital District of Southwest Finland, Turku, Finland); Oili Kaipiainen-Seppänen (Northern Savo Hospital District, Kuopio, Finland); Johanna Huhtakangas (Northern Savo Hospital District, Kuopio, Finland); Ali Abbasi (Abbvie, Chicago, IL, United States); Jeffrey Waring (Abbvie, Chicago, IL, United States) Fedik Rahimov (Abbvie, Chicago, IL, United States); Apinya Lertratanakul (Abbvie, Chicago, IL, United States); Nizar Smaoui (Abbvie, Chicago, IL, United States); Anne Lehtonen (Abbvie, Chicago, IL, United States); Adam Platt (Astra Zeneca, Cambridge, United Kingdom); David Close (Astra Zeneca, Cambridge, United Kingdom); Marla Hochfeld (Celgene, Summit, NJ, United States/Bristol Myers Squibb, New York, NY, United States); Natalie Bowers (Genentech, San Francisco, CA, United States); Sarah Pendergrass Genentech, San Francisco, CA, United States); Onuralp Soylemez (Merck, Kenilworth, NJ, United States); Kirsi Kalpala (Pfizer, New York, NY, United States); Nan Bing (Pfizer, New York, NY, United States); Xinli Hu (Pfizer, New York, NY, United States); Kirsi Auro (GlaxoSmithKline, Brentford, United Kingdom); Dawn Waterworth (Janssen Biotech, Beerse, Belgium); Andrea Ganna (Institute for Molecular Medicine Finland, HiLIFE, Helsinki, Finland, Finland); Anne Kerola (University of Helsinki); Hanna-Kaisa Heikkilä (Pirkanmaa Hospital District, Tampere, Finland); Javier Gracia (Tabuenca University of Tampere); Johanna Hiltunen (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Johanna Paltta (Hospital District of Southwest Finland, Turku, Finland); Juha Sinisalo (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Jukka Koskela (Institute for Molecular Medicine Finland, HiLIFE, Helsinki, Finland, Finland); Nina Mars (Institute for Molecular Medicine Finland, HiLIFE, Helsinki, Finland, Finland); Tarja Laitinen (University of Tampere); Tuulikki Sokka-Isler (Jyväskylä Central Hospital); Vincent Llorens (Institute for Molecular Medicine Finland, HiLIFE, Helsinki, Finland, Finland). FinnGen: Steering Committee: Aarno Palotie (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Mark Daly (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland). Pharmaceutical companies: Bridget Riley-Gills (Abbvie, Chicago, IL, United States); Howard Jacob (Abbvie, Chicago, IL, United States); Dirk Paul (Astra Zeneca, Cambridge, United Kingdom); Heiko Runz (Biogen, Cambridge, MA, United States);Sally John (Biogen, Cambridge, MA, United States); Robert Plenge (Celgene, Summit, NJ, United States/Bristol Myers Squibb, New York, NY, United States); Mark McCarthy (Genentech, San Francisco, CA, United States); Julie Hunkapiller (Genentech, San Francisco, CA, United States); Meg Ehm (GlaxoSmithKline, Brentford, United Kingdom); Kirsi Auro (GlaxoSmithKline, Brentford, United Kingdom); Caroline Fox (Merck, Kenilworth, NJ, United States); Anders Mälarstig (Pfizer, New York, NY, United States); Katherine Klinger (Sanofi, Paris, France); Deepak Raipal (Sanofi, Paris, France); Tim Behrens (Maze Therapeutics, San Francisco, CA, United States); Robert Yang (Janssen Biotech, Beerse, Belgium); Richard Siegel (Novartis, Basel, Switzerland). University of Helsinki & Biobanks: Tomi Mäkelä (HiLIFE, University of Helsinki, Finland, Finland); Jaakko Kaprio (Institute for Molecular Medicine Finland, HiLIFE, Helsinki, Finland, Finland); Petri Virolainen (Auria Biobank / University of Turku / Hospital District of Southwest Finland, Turku, Finland); Antti Hakanen (Auria Biobank / University of Turku / Hospital District of Southwest Finland, Turku, Finland); Terhi Kilpi (THL Biobank / The National Institute of Health and Welfare Helsinki, Finland); Markus Perola (THL Biobank / The National Institute of Health and Welfare Helsinki, Finland); Jukka Partanen (Finnish Red Cross Blood Service / Finnish Hematology Registry and Clinical Biobank, Helsinki, Finland); Anne Pitkäranta (Helsinki Biobank / Helsinki University and Hospital District of Helsinki and Uusimaa, Helsinki); Juhani Junttila (Northern Finland Biobank Borealis / University of Oulu / Northern Ostrobothnia Hospital District, Oulu, Finland); Raisa Serpi (Northern Finland Biobank Borealis / University of Oulu / Northern Ostrobothnia Hospital District, Oulu, Finland); Tarja Laitinen (Finnish Clinical Biobank Tampere / University of Tampere / Pirkanmaa Hospital District, Tampere, Finland); Johanna Mäkelä (Finnish Clinical Biobank Tampere / University of Tampere / Pirkanmaa Hospital District, Tampere, Finland); Veli-Matti Kosma (Biobank of Eastern Finland / University of Eastern Finland / Northern Savo Hospital District, Kuopio, Finland); Urho Kujala (Central Finland Biobank / University of Jyväskylä / Central Finland Health Care District, Jyväskylä, Finland); Other Experts/ Non-Voting Members: Outi Tuovila (Business Finland, Helsinki, Finland); Raimo Pakkanen (Business Finland, Helsinki, Finland). Scientific Committee Pharmaceutical companies: Jeffrey Waring (Abbvie, Chicago, IL, United States); Ali Abbasi (Abbvie, Chicago, IL, United States); Mengzhen Liu (Abbvie, Chicago, IL, United States); Ioanna Tachmazidou (Astra Zeneca, Cambridge, United Kingdom); Chia-Yen Chen (Biogen, Cambridge, MA, United States); Heiko Runz (Biogen, Cambridge, MA, United States); Shameek Biswas (Celgene, Summit, NJ, United States/Bristol Myers Squibb, New York, NY, United States); Julie Hunkapiller (Genentech, San Francisco, CA, United States); Meg Ehm (GlaxoSmithKline, Brentford, United Kingdom); Neha Raghavan (Merck, Kenilworth, NJ, United States); Adriana Huertas-Vazquez (Merck, Kenilworth, NJ, United States); Anders Mälarstig (Pfizer, New York, NY, United States); Xinli Hu (Pfizer, New York, NY, United States); Katherine Klinger (Sanofi, Paris, France); Matthias Gossel (Sanofi, Paris, France); Robert Graham (Maze Therapeutics, San Francisco, CA, United States); Tim Behrens (Maze Therapeutics, San Francisco, CA, United States); Beryl Cummings (Maze Therapeutics, San Francisco, CA, United States); Wilco Fleuren (Janssen Biotech, Beerse, Belgium); Dawn Waterworth (Janssen Biotech, Beerse, Belgium); Nicole Renaud (Novartis, Basel, Switzerland); Ma'en Obeidat (Novartis, Basel, Switzerland). University of Helsinki & Biobanks: Samuli Ripatti (Institute for Molecular Medicine Finland, HiLIFE, Helsinki, Finland); Johanna Schleutker (Auria Biobank / Univ. of Turku / Hospital District of Southwest Finland, Turku, Finland); Markus Perola (THL Biobank / The National Institute of Health and Welfare Helsinki, Finland); Mikko Arvas (Finnish Red Cross Blood Service / Finnish Hematology Registry and Clinical Biobank, Helsinki, Finland); Olli Carpén (Helsinki Biobank / Helsinki University and Hospital District of Helsinki and Uusimaa, Helsinki); Reetta Hinttala (Northern Finland Biobank Borealis / University of Oulu / Northern Ostrobothnia Hospital District, Oulu, Finland); Johannes Kettunen (Northern Finland Biobank Borealis / University of Oulu / Northern Ostrobothnia Hospital District, Oulu, Finland); Johanna Mäkelä (Finnish Clinical Biobank Tampere / University of Tampere / Pirkanmaa Hospital District, Tampere, Finland); Arto Mannermaa (Biobank of Eastern Finland / University of Eastern Finland / Northern Savo Hospital District, Kuopio, Finland); Jari Laukkanen (Central Finland Biobank / University of Jyväskylä / Central Finland Health Care District, Jyväskylä, Finland); Urho Kujala (Central Finland Biobank / University of Jyväskylä / Central Finland Health Care District, Jyväskylä, Finland). Clinical Groups: Neurology Group: Reetta Kälviäinen (Northern Savo Hospital District, Kuopio, Finland); Valtteri Julkunen (Northern Savo Hospital District, Kuopio, Finland); Hilkka Soininen (Northern Savo Hospital District, Kuopio, Finland); Anne Remes (Northern Ostrobothnia Hospital District, Oulu, Finland); Mikko Hiltunen (Northern Savo Hospital District, Kuopio, Finland); Jukka Peltola (Pirkanmaa Hospital District, Tampere, Finland); Pentti Tienari (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Juha Rinne (Hospital District of Southwest Finland, Turku, Finland); Roosa Kallionpää (Hospital District of Southwest Finland, Turku, Finland); Ali Abbasi (Abbvie, Chicago, IL, United States); Adam Ziemann (Abbvie, Chicago, IL, United States); Jeffrey Waring (Abbvie, Chicago, IL, United States); Sahar Esmaeeli (Abbvie, Chicago, IL, United States); Nizar Smaoui (Abbvie, Chicago, IL, United States); Anne Lehtonen (Abbvie, Chicago, IL, United States); Susan Eaton (Biogen, Cambridge, MA, United States); Heiko Runz (Biogen, Cambridge, MA, United States); Sanni Lahdenperä (Biogen, Cambridge, MA, United States); Janet van Adelsberg (Celgene, Summit, NJ, United States/ Bristol Myers Squibb, New York, NY, United States); Shameek Biswas (Celgene, Summit, NJ, United States/ Bristol Myers Squibb, New York, NY, United States); Julie Hunkapiller (Genentech, San Francisco, CA, United States); Natalie Bowers (Genentech, San Francisco, CA, United States); Edmond Teng (Genentech, San Francisco, CA, United States); Sarah Pendergrass (Genentech, San Francisco, CA, United States); Onuralp Soylemez (Merck, Kenilworth, NJ, United States); Kari Linden (Pfizer, New York, NY, United States); Fanli Xu (GlaxoSmithKline, Brentford, United Kingdom); David Pulford (GlaxoSmithKline, Brentford, United Kingdom); Kirsi Auro (GlaxoSmithKline, Brentford, United Kingdom); Laura Addis (GlaxoSmithKline, Brentford, United Kingdom); John Eicher (GlaxoSmithKline, Brentford, United Kingdom); Minna Raivio (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Sarah Pendergrass (Genentech, San Francisco, CA, United States); Beryl Cummings (Maze Therapeutics, San Francisco, CA, United States); Juulia Partanen (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland). Gastroenterology Group: Martti Färkkilä (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Jukka Koskela (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Sampsa Pikkarainen (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Airi Jussila (Pirkanmaa Hospital District, Tampere, Finland); Katri Kaukinen (Pirkanmaa Hospital District, Tampere, Finland); Timo Blomster (Northern Ostrobothnia Hospital District, Oulu, Finland); Mikko Kiviniemi (Northern Savo Hospital District, Kuopio, Finland); Markku Voutilainen (Hospital District of Southwest Finland, Turku, Finland); Ali Abbasi (Abbvie, Chicago, IL, United States); Graham Heap (Abbvie, Chicago, IL, United States); Jeffrey Waring (Abbvie, Chicago, IL, United States); Nizar Smaoui (Abbvie, Chicago, IL, United States); Fedik Rahimov (Abbvie, Chicago, IL, United States); Anne Lehtonen (Abbvie, Chicago, IL, United States); Keith

Ann Rheum Dis: first published as 10.1136/annrheumdis-2021-220698 on 3 August 2021. Downloaded from http://ard.bmj.com/ on December 14, 2021 at University of Helsinki. Protected by copyright.

Usiskin (Celgene, Summit, NJ, United States/ Bristol Myers Squibb, New York, NY, United States); Tim Lu (Genentech, San Francisco, CA, United States); Natalie Bowers (Genentech, San Francisco, CA, United States); Danny Oh (Genentech, San Francisco, CA, United States); Sarah Pendergrass (Genentech, San Francisco, CA, United States); Kirsi Kalpala (Pfizer, New York, NY, United States); Melissa Miller (Pfizer, New York, NY, United States); Xinli Hu (Pfizer, New York, NY, United States); Linda McCarthy (GlaxoSmithKline, Brentford, United Kingdom); Onuralp Soylemez (Merck, Kenilworth, NJ, United States); Mark Daly (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland). Pulmonology Group: Tarja Laitinen (Pirkanmaa Hospital District, Tampere, Finland); Margit Pelkonen (Northern Savo Hospital District, Kuopio, Finland); Paula Kauppi (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Hannu Kankaanranta (Pirkanmaa Hospital District, Tampere, Finland); Terttu Harju (Northern Ostrobothnia Hospital District, Oulu, Finland); Riitta Lahesmaa (Hospital District of Southwest Finland, Turku, Finland); Nizar Smaoui (Abbvie, Chicago, IL, United States); Alex Mackay (Astra Zeneca, Cambridge, United Kingdom); Glenda Lassi (Astra Zeneca, Cambridge, United Kingdom); Susan Eaton (Biogen, Cambridge, MA, United States); Steven Greenberg (Celgene, Summit, NJ, United States/ Bristol Myers Squibb, New York, NY, United States); Hubert Chen (Genentech, San Francisco, CA, United States); Sarah Pendergrass (Genentech, San Francisco, CA, United States); Natalie Bowers (Genentech, San Francisco, CA, United States); Joanna Betts (GlaxoSmithKline, Brentford, United Kingdom); Soumitra Ghosh (GlaxoSmithKline, Brentford, United Kingdom); Kirsi Auro (GlaxoSmithKline, Brentford, United Kingdom); Rajashree Mishra (GlaxoSmithKline, Brentford, United Kingdom); Sina Rüeger (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland). Cardiometabolic Diseases Group: Teemu Niiranen (The National Institute of Health and Welfare Helsinki, Finland); Felix Vaura (The National Institute of Health and Welfare Helsinki, Finland); Veikko Salomaa (The National Institute of Health and Welfare Helsinki, Finland); Markus Juonala (Hospital District of Southwest Finland, Turku, Finland); Kaj Metsärinne (Hospital District of Southwest Finland, Turku, Finland); Mika Kähönen (Pirkanmaa Hospital District, Tampere, Finland); Juhani Junttila (Northern Ostrobothnia Hospital District, Oulu, Finland); Markku Laakso (Northern Savo Hospital District, Kuopio, Finland); Jussi Pihlajamäki (Northern Savo Hospital District, Kuopio, Finland); Daniel Gordin (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Juha Sinisalo (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Marja-Riitta (Taskinen Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Tiinamaija Tuomi (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Jari Laukkanen (Central Finland Health Care District, Jyväskylä, Finland); Benjamin Challis (Astra Zeneca, Cambridge, United Kingdom); Dirk Paul (Astra Zeneca, Cambridge, United Kingdom); Julie Hunkapiller (Genentech, San Francisco, CA, United States); Natalie Bowers (Genentech, San Francisco, CA, United States); Sarah Pendergrass (Genentech, San Francisco, CA, United States); Onuralp Soylemez (Merck, Kenilworth, NJ, United States); Jaakko Parkkinen (Pfizer, New York, NY, United States); Melissa Miller (Pfizer, New York, NY, United States); Russell Miller (Pfizer, New York, NY, United States); Audrey Chu (GlaxoSmithKline, Brentford, United Kingdom); Kirsi Auro (GlaxoSmithKline, Brentford, United Kingdom); Keith Usiskin (Celgene, Summit, NJ, United States/ Bristol Myers Squibb, New York, NY, United States); Amanda Elliott (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland / Broad Institute, Cambridge, MA, United States); Joel Rämö (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Samuli Ripatti (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Mary Pat Reeve (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Sanni Ruotsalainen (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland). Oncology Group: Tuomo Meretoja (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Heikki Joensuu (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Olli Carpén (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Lauri Aaltonen (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Johanna Mattson (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Annika Auranen (Pirkanmaa Hospital District, Tampere, Finland); Peeter Karihtala (Northern Ostrobothnia Hospital District, Oulu, Finland); Saila Kauppila (Northern Ostrobothnia Hospital District, Oulu, Finland); Päivi Auvinen (Northern Savo Hospital District, Kuopio, Finland); Klaus Elenius (Hospital District of Southwest Finland, Turku, Finland); Johanna Schleutker (Hospital District of Southwest Finland, Turku, Finland); Relja Popovic (Abbvie, Chicago, IL, United States); Jeffrey Waring (Abbvie, Chicago, IL, United States); Bridget Riley-Gillis (Abbvie, Chicago, IL, United States); Anne Lehtonen (Abbvie, Chicago, IL, United States); Jennifer Schutzman (Genentech, San Francisco, CA, United States); Julie Hunkapiller (Genentech, San Francisco, CA, United States); Natalie Bowers (Genentech, San Francisco, CA, United States); Sarah Pendergrass (Genentech, San Francisco, CA, United States); Andrey Loboda (Merck, Kenilworth, NJ, United States); Aparna Chhibber (Merck, Kenilworth, NJ, United States); Heli Lehtonen (Pfizer, New York, NY, United States); Stefan McDonough (Pfizer, New York, NY, United States); Marika Crohns (Sanofi, Paris, France); Sauli Vuoti (Sanofi, Paris, France); Diptee Kulkarni (GlaxoSmithKline, Brentford, United Kingdom); Kirsi Auro (GlaxoSmithKline, Brentford, United Kingdom); Esa Pitkänen (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Nina Mars (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Mark Daly (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland). Opthalmology Group: Kai Kaarniranta (Northern Savo Hospital District, Kuopio, Finland); Joni A Turunen (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Terhi Ollila (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Sanna Seitsonen (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Hannu Uusitalo (Pirkanmaa Hospital District, Tampere, Finland); Vesa Aaltonen (Hospital District of Southwest Finland, Turku, Finland); Hannele Uusitalo-Järvinen (Pirkanmaa Hospital District, Tampere, Finland); Marja Luodonpää (Northern Ostrobothnia Hospital District, Oulu, Finland); Nina Hautala (Northern Ostrobothnia Hospital District, Oulu, Finland); Mengzhen Liu (Abbvie, Chicago, IL, United States); Heiko Runz (Biogen, Cambridge, MA, United States); Stephanie Loomis (Biogen, Cambridge, MA, United States); Erich Strauss (Genentech, San Francisco, CA, United States); Natalie Bowers (Genentech, San Francisco, CA, United States); Hao Chen (Genentech, San Francisco, CA, United States); Sarah Pendergrass (Genentech, San Francisco, CA, United States); Anna Podgornaia (Merck, Kenilworth, NJ, United States); Juha Karjalainen (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland / Broad Institute, Cambridge, MA, United States); Esa Pitkänen (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland). Dermatology Group: Kaisa Tasanen (Northern Ostrobothnia Hospital District, Oulu, Finland); Laura Huilaja (Northern Ostrobothnia Hospital District, Oulu, Finland); Katariina Hannula-Jouppi (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Teea Salmi (Pirkanmaa Hospital District, Tampere, Finland); Sirkku Peltonen (Hospital District of Southwest Finland, Turku, Finland); Leena Koulu (Hospital District of Southwest Finland, Turku, Finland); Kirsi Kalpala (Pfizer, New York, NY, United States); Ying Wu (Pfizer, New York, NY, United States); David Choy (Genentech, San Francisco, CA, United States); Sarah Pendergrass (Genentech, San Francisco, CA, United States); Nizar Smaoui (Abbvie, Chicago, IL, United States); Fedik Rahimov (Abbvie, Chicago, IL, United States); Anne Lehtonen (Abbvie, Chicago, IL, United States); Dawn Waterworth (Janssen Biotech, Beerse, Belgium); Odontology Group: Pirkko Pussinen (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Aino Salminen (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Tuula Salo (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); David Rice (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Pekka Nieminen (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Ulla Palotie (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Juha Sinisalo (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Maria Siponen (Northern Savo Hospital District, Kuopio, Finland); Liisa Suominen (Northern Savo Hospital District, Kuopio, Finland); Päivi Mäntylä (Northern Savo Hospital District, Kuopio, Finland); Ulvi Gursoy (Hospital District of Southwest Finland, Turku, Finland); Vuokko Anttonen (Northern Ostrobothnia Hospital District, Oulu, Finland); Kirsi Sipilä (Northern Ostrobothnia Hospital District, Oulu, Finland); Sarah Pendergrass (Genentech, San Francisco, CA, United States); Women's Health and Reproduction Group: Hannele Laivuori (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Venla Kurra (Pirkanmaa Hospital District, Tampere, Finland); Oskari Heikinheimo (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Ilkka Kalliala (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Laura Kotaniemi-Talonen (Pirkanmaa Hospital District, Tampere, Finland); Kari Nieminen (Pirkanmaa Hospital District, Tampere, Finland); Päivi Polo (Hospital District of Southwest Finland, Turku, Finland); Kaarin Mäkikallio (Hospital District of Southwest Finland, Turku, Finland); Eeva Ekholm (Hospital District of Southwest Finland, Turku, Finland); Marja Vääräsmäki (Northern Ostrobothnia Hospital District, Oulu, Finland); Outi Uimari (Northern Ostrobothnia Hospital District, Oulu, Finland); Laure Morin-Papunen (Northern Ostrobothnia Hospital District, Oulu, Finland); Marjo Tuppurainen (Northern Savo Hospital District, Kuopio, Finland); Katja Kivinen (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Elisabeth Widen (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Taru Tukiainen (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Mary Pat Reeve (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Mark Daly (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Liu Aoxing (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Eija Laakkonen (University of Jyväskylä, Jyväskylä, Finland); Niko Välimäki (University of Helsinki, Helsinki, Finland); Lauri Aaltonen (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Johannes Kettunen (Northern Ostrobothnia Hospital District, Oulu, Finland); Mikko Arvas (Finnish Red Cross Blood Service, Helsinki, Finland); Jeffrey Waring (Abbvie, Chicago, IL, United States); Bridget Riley-Gillis (Abbvie, Chicago, IL, United States); Mengzhen Liu (Abbvie, Chicago, IL, United States); Janet Kumar (GlaxoSmithKline, Brentford, United Kingdom); Kirsi Auro (GlaxoSmithKline, Brentford, United Kingdom); Andrea Ganna (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Sarah Pendergrass (Genentech, San Francisco, CA, United States); FinnGen Analysis working group: Justin Wade Davis (Abbvie, Chicago, IL, United States); Bridget Riley-Gillis (Abbvie, Chicago, IL, United States); Danjuma Quarless (Abbvie, Chicago, IL, United States); Fedik Rahimov (Abbvie, Chicago, IL, United States); Sahar Esmaeeli (Abbvie, Chicago, IL, United States); Slavé Petrovski (Astra Zeneca, Cambridge, United Kingdom); Eleonor Wigmore (Astra Zeneca, Cambridge, United Kingdom); Adele Mitchell (Biogen, Cambridge, MA, United States); Benjamin Sun (Biogen, Cambridge, MA, United States); Ellen Tsai (Biogen, Cambridge, MA, United States); Denis Baird (Biogen, Cambridge, MA, United States); Paola Bronson (Biogen, Cambridge, MA, United States); Ruoyu Tian (Biogen, Cambridge, MA, United States); Stephanie Loomis (Biogen, Cambridge, MA,

Ann Rheum Dis: first published as 10.1136/annrheumdis-2021-220698 on 3 August 2021. Downloaded from http://ard.bmj.com/ on December 14, 2021 at University of Helsinki. Protected by copyright.

United States); Yunfeng Huang (Biogen, Cambridge, MA, United States); Joseph Maranville (Celgene, Summit, NJ, United States/ Bristol Myers Squibb, New York, NY, United States); Shameek Biswas (Celgene, Summit, NJ, United States/ Bristol Myers Squibb, New York, NY, United States); Elmutaz Mohammed (Celgene, Summit, NJ, United States/ Bristol Myers Squibb, New York, NY, United States); Samir Wadhawan (Celgene, Summit, NJ, United States/ Bristol Myers Squibb, New York, NY, United States); Erika Kvikstad (Celgene, Summit, NJ, United States/ Bristol Myers Squibb, New York, NY, United States); Minal Caliskan (Celgene, Summit, NJ, United States/ Bristol Myers Squibb, New York, NY, United States); Diana Chang (Genentech, San Francisco, CA, United States); Julie Hunkapiller (Genentech, San Francisco, CA, United States); Tushar Bhangale (Genentech, San Francisco, CA, United States); Natalie Bowers (Genentech, San Francisco, CA, United States); Sarah Pendergrass (Genentech, San Francisco, CA, United States); Kirill Shkura (Merck, Kenilworth, NJ, United States); Victor Neduva (Merck, Kenilworth, NJ, United States); Xing Chen (Pfizer, New York, NY, United States); Åsa Hedman (Pfizer, New York, NY, United States); Karen S King (GlaxoSmithKline, Brentford, United Kingdom); Padhraig Gormley (GlaxoSmithKline, Brentford, United Kingdom); Jimmy Liu (GlaxoSmithKline, Brentford, United Kingdom); Clarence Wang (Sanofi, Paris, France); Ethan Xu (Sanofi, Paris, France); Franck Auge (Sanofi, Paris, France); Clement Chatelain (Sanofi, Paris, France); Deepak Rajpal (Sanofi, Paris, France); Dongyu Liu (Sanofi, Paris, France); Katherine Call (Sanofi, Paris, France); Tai-He Xia (Sanofi, Paris, France); Beryl Cummings (Maze Therapeutics, San Francisco, CA, United States); Matt Brauer (Maze Therapeutics, San Francisco, CA, United States); Huilei Xu (Novartis, Basel, Switzerland); Amy Cole (Novartis, Basel, Switzerland); Jonathan Chung (Novartis, Basel, Switzerland); Jaison Jacob (Novartis, Basel, Switzerland); Katrina de Lange (Novartis, Basel, Switzerland); Jonas Zierer (Novartis, Basel, Switzerland); Mitja Kurki (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland / Broad Institute, Cambridge, MA, United States); Samuli Ripatti (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Mark Daly (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Juha Karjalainen (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland / Broad Institute, Cambridge, MA, United States); Aki Havulinna (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Juha Mehtonen (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Priit Palta (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Shabbeer Hassan (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Pietro Della Briotta Parolo (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Wei Zhou (Broad Institute, Cambridge, MA, United States); Mutaamba Maasha (Broad Institute, Cambridge, MA, United States); Shabbeer Hassan (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Susanna Lemmelä (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Manuel Rivas (University of Stanford, Stanford, CA, United States); Aarno Palotie (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Arto Lehisto (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Andrea Ganna (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Vincent Llorens (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Hannele Laivuori (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Mari E Niemi (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Taru Tukiainen (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Mary Pat Reeve (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Henrike Heyne (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Nina Mars (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Kimmo Palin (University of Helsinki, Helsinki, Finland); Javier Garcia-Tabuenca (University of Tampere, Tampere, Finland); Harri Siirtola (University of Tampere, Tampere, Finland); Tuomo Kiiskinen (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Jiwoo Lee (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland / Broad Institute, Cambridge, MA, United States); Kristin Tsuo (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland / Broad Institute, Cambridge, MA, United States); Amanda Elliott (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland / Broad Institute, Cambridge, MA, United States); Kati Kristiansson (THL Biobank / The National Institute of Health and Welfare Helsinki, Finland Mikko Arvas Finnish Red Cross Blood Service / Finnish Hematology Registry and Clinical Biobank, Helsinki, Finland); Kati Hyvärinen (Finnish Red Cross Blood Service, Helsinki, Finland); Jarmo Ritari (Finnish Red Cross Blood Service, Helsinki, Finland); Miika Koskinen (Helsinki Biobank / Helsinki University and Hospital District of Helsinki and Uusimaa, Helsinki); Olli Carpén (Helsinki Biobank / Helsinki University and Hospital District of Helsinki and Uusimaa, Helsinki); Johannes Kettunen (Northern Finland Biobank Borealis / University of Oulu / Northern Ostrobothnia Hospital District, Oulu, Finland); Katri Pylkäs (University of Oulu, Oulu, Finland); Marita Kalaoja (University of Oulu, Oulu, Finland); Minna Karjalainen (University of Oulu, Oulu, Finland); Tuomo Mantere (Northern Finland Biobank Borealis / University of Oulu / Northern Ostrobothnia Hospital District, Oulu, Finland); Eeva Kangasniemi (Finnish Clinical Biobank Tampere / University of Tampere / Pirkanmaa Hospital District, Tampere, Finland); Sami Heikkinen (University of Eastern Finland, Kuopio, Finland); Arto Mannermaa (Biobank of Eastern Finland / University of Eastern Finland / Northern Savo Hospital District, Kuopio, Finland); Eija Laakkonen (University of Jyväskylä, Jyväskylä, Finland); Samuel Heron (University of Turku, Turku, Finland); Dhanaprakash Jambulingam (University of Turku, Turku, Finland); Venkat Subramaniam Rathinakannan (University of Turku, Turku, Finland); Nina Pitkänen (Auria Biobank / University of Turku / Hospital District of Southwest Finland, Turku, Finland). Biobank directors Lila Kallio (Auria Biobank / University of Turku / Hospital District of Southwest Finland, Turku, Finland); Sirpa Soini (THL Biobank / The National Institute of Health and Welfare Helsinki, Finland); Jukka Partanen (Finnish Red Cross Blood Service / Finnish Hematology Registry and Clinical Biobank, Helsinki, Finland); Eero Punkka (Helsinki Biobank / Helsinki University and Hospital District of Helsinki and Uusimaa, Helsinki); Raisa Serpi (Northern Finland Biobank Borealis / University of Oulu / Northern Ostrobothnia Hospital District, Oulu, Finland); Johanna Mäkelä (Finnish Clinical Biobank Tampere / University of Tampere / Pirkanmaa Hospital District, Tampere, Finland); Veli-Matti Kosma (Biobank of Eastern Finland / University of Eastern Finland / Northern Savo Hospital District, Kuopio, Finland); Teijo Kuopio (Central Finland Biobank / University of Jyväskylä / Central Finland Health Care District, Jyväskylä, Finland); FinnGen Teams: Administration: Anu Jalanko (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Huei-Yi Shen (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Risto Kajanne (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Mervi Aavikko (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Analysis: Mitja Kurki (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland / Broad Institute, Cambridge, MA, United States); Juha Karjalainen (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland / Broad Institute, Cambridge, MA, United States); Pietro Della Briotta Parolo (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Arto Lehisto (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Juha Mehtonen (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Wei Zhou (Broad Institute, Cambridge, MA, United States); Masahiro Kanai (Broad Institute, Cambridge, MA, United States); Mutaamba Maasha (Broad Institute, Cambridge, MA, United States); Clinical Endpoint Development: Hannele Laivuori (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Aki Havulinna (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Susanna Lemmelä (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Tuomo Kiiskinen (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); L. Elisa Lahtela (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Matti Peura (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Communication: Mari Kaunisto (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Data Management and IT Infrastructure: Elina Kilpeläinen (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Timo P. Sipilä (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Georg Brein (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Oluwaseun A. Dada (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Awaisa Ghazal (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Anastasia Shcherban (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland). Genotyping: Kati Donner (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Timo P. Sipilä (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland). Sample Collection Coordination: Anu Loukola Helsinki Biobank / Helsinki University and Hospital District of Helsinki and Uusimaa, Helsinki. Sample Logistics: Päivi Laiho (THL Biobank / The National Institute of Health and Welfare Helsinki, Finland); Tuuli Sistonen (THL Biobank / The National Institute of Health and Welfare Helsinki, Finland); Essi Kaiharju (THL Biobank / The National Institute of Health and Welfare Helsinki, Finland); Markku Laukkanen (THL Biobank / The National Institute of Health and Welfare Helsinki, Finland). Elina Järvensivu (THL Biobank / The National Institute of Health and Welfare Helsinki, Finland); Sini Lähteenmäki (THL Biobank / The National Institute of Health and Welfare Helsinki, Finland); Lotta Männikkö (THL Biobank / The National Institute of Health and Welfare Helsinki, Finland); Regis Wong (THL Biobank / The National Institute of Health and Welfare Helsinki, Finland). Registry Data Operations: Hannele Mattsson (THL Biobank / The National Institute of Health and Welfare Helsinki, Finland); Kati Kristiansson (THL Biobank / The National Institute of Health and Welfare Helsinki, Finland); Susanna Lemmelä (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Sami Koskelainen (THL Biobank / The National Institute of Health and Welfare Helsinki, Finland); Tero Hiekkalinna (THL Biobank / The National Institute of Health and Welfare Helsinki, Finland); Teemu Paajanen (THL Biobank / The National Institute of Health and Welfare Helsinki, Finland). Sequencing Informatics: Priit Palta (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Kalle Pärn (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Shuang Luo (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Vishal Sinha (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland); Trajectory Team: Tarja Laitinen (Pirkanmaa Hospital District, Tampere, Finland); Harri Siirtola (University of Tampere, Tampere, Finland); Javier Gracia-Tabuenca (University of Tampere, Tampere, Finland); Mika Helminen (University of Tampere, Tampere, Finland); Tiina Luukkaala (University of Tampere, Tampere, Finland); Iida Vähätalo (University of Tampere, Tampere, Finland). Data protection

Ann Rheum Dis: first published as 10.1136/annrheumdis-2021-220698 on 3 August 2021. Downloaded from http://ard.bmj.com/ on December 14, 2021 at University of Helsinki. Protected by copyright.

officer: Tero Jyrhämä (Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Finland). FinBB - Finnish biobank cooperative: Marco Hautalahti, Laura Mustaniemi, Mirkka Koivusalo, Sarah Smith, Tom Southerington.

Contributors AnttiP and NM conceived and designed the study. NM carried out the statistical and computational analyses with advice from SR and AnttiP. All authors provided critical inputs to interpretation of the data. The manuscript was written and revised by NM and AnttiP with comments from all of the coauthors. All coauthors have approved the final version of the manuscript.

Funding This work was supported by Turku University Hospital Research Foundation (to AnttiP), the Sigrid Jusélius Foundation (to SR and AarnoP); Foundation and the Horizon 2020 Research and Innovation Programme [grant number 667301 (COSYN) to AarnoP]; University of Helsinki HiLIFE Fellow grants 2017-2020 (to SR); Academy of Finland Center of Excellence in Complex Disease Genetics (grant number 312062 to SR, 312074 to AarnoP); Academy of Finland (grant number 331671 to NM, grant number 285380 to SR, 334229 to JK and TL). This study is part of the FinnGen project funded by Business Finland (grant numbers HUS 4685/31/2016 and UH 4386/31/2016) and 12 pharma companies: AbbVie Inc, AstraZeneca UK Ltd, Biogen MA Inc, Celgene Corporation, Celgene International II Sàrl, Genentech Inc, Merck Sharp & Dohme Corp, Pfizer Inc, GlaxoSmithKline Intellectual Property Development Ltd, Sanofi US Services Inc, Maze Therapeutics Inc, Janssen Biotech Inc and Novartis AG.

Competing interests AnttiP has received a consulting fee from Pfizer and Abbvie, a lecture fee from Pfizer and Sanofi, and support for attending a meeting from Bristol-Myers-Squib and Novartis. JK has received a consulting fee and a lecture fee from Pfizer. TL has received consulting fee and lecture fee from Pfizer. The other authors declare no competing interests.

Patient consent for publication Not required.

Ethics approval Patients and control subjects in FinnGen provided informed consent for biobank research, based on the Finnish Biobank Act. Alternatively, separate research cohorts, collected prior the Finnish Biobank Act came into effect (in September 2013) and start of FinnGen (August 2017), were collected based on study-specific consents and later transferred to the Finnish biobanks after approval by Fimea, the National Supervisory Authority for Welfare and Health. Recruitment protocols followed the biobank protocols approved by Fimea. The Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa (HUS) approved the FinnGen study protocol Nr HUS/990/2017. The FinnGen study is approved by Finnish Institute for Health and Welfare (permit numbers: THL/2031/6.02.00/2017, THL/1101/5.05.00/2017, THL/341/6.02.00/2018, THL/2222/6.02.00/2018, THL/283/6.02.00/2019, THL/1721/5.05.00/2019, THL/1524/5.05.00/2020 and THL/2364/14.02/2020), Digital and population data service agency (permit numbers: VRK43431/2017-3, VRK/6909/2018-3, VRK/4415/2019-3), the Social Insurance Institution (permit numbers: KELA 58/522/2017, KELA 131/522/2018, KELA 70/522/2019, KELA 98/522/2019, KELA 138/522/2019, KELA 2/522/2020, KELA 16/522/2020 and Statistics Finland (permit numbers: TK-53-1041-17 and TK-53-90-20).This analysis was conducted with the UK Biobank Resource under Application Number 22627. The Biobank Access Decisions for FinnGen samples and data utilized in FinnGen Data Freeze 7 include: THL Biobank BB2017_55, BB2017_111, BB2018_19, BB_2018_34, BB_2018_67, BB2018_71, BB2019_7, BB2019_8, BB2019_26, BB2020_1, Finnish Red Cross Blood Service Biobank 7.12.2017, Helsinki Biobank HUS/359/2017, Auria Biobank AB17-5154 and amendment #1 (August 17 2020), Biobank Borealis of Northern Finland_2017_1013, Biobank of Eastern Finland 1186/2018 and amendment 22 § /2020, Finnish Clinical Biobank Tampere MH0004 and amendments (21.02.2020 & 06.10.2020), Central Finland Biobank 1-2017, and Terveystalo Biobank STB 2018001. The UK Biobank analysis was conducted with the UK Biobank Resource under Application Number 22627.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The Finnish biobank data can be accessed through the Fingenious® services (https://site.fingenious.fi/en/) managed by FINBB. The remaining data are available within the article, supplemental information or available from the authors upon request.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: https://creativecommons.org/licenses/by/4.0/.

ORCID iDs
Antti Palomäki http://orcid.org/0000-0002-8835-8116
Nina Mars http://orcid.org/0000-0002-7259-5993

REFERENCES

1 Myasoedova E, Crowson CS, Turesson C, *et al*. Incidence of extraarticular rheumatoid arthritis in Olmsted County, Minnesota, in 1995-2007 versus 1985-1994: a population-based study. J Rheumatol 2011;38:983–9.
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 2010;49:1483–9.
3 Bongartz T, Nannini C, Medina-Velasquez YF, *et al*. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. Arthritis Rheum 2010;62:1583–91.
4 Olson AL, Swigris JJ, Sprunger DB, *et al*. Rheumatoid arthritis-interstitial lung disease-associated mortality. Am J Respir Crit Care Med 2011;183:372–8.
5 Dawson JK, Fewins HE, Desmond J, *et al*. Fibrosing alveolitis in patients with rheumatoid arthritis as assessed by high resolution computed tomography, chest radiography, and pulmonary function tests. Thorax 2001;56:622–7.
6 Gabbay E, Tarala R, Will R, *et al*. Interstitial lung disease in recent onset rheumatoid arthritis. Am J Respir Crit Care Med 1997;156:528–35.
7 Gochuico BR, Avila NA, Chow CK, *et al*. Progressive preclinical interstitial lung disease in rheumatoid arthritis. Arch Intern Med 2008;168:159–66.
8 Hyldgaard C, Hilberg O, Pedersen AB, *et al*. A population-based cohort study of rheumatoid arthritis-associated interstitial lung disease: comorbidity and mortality. Ann Rheum Dis 2017;76:1700–6.
9 Kelly CA, Saravanan V, Nisar M, *et al*. Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics--a large multicentre UK study. Rheumatology 2014;53:1676–82.
10 Seibold MA, Wise AL, Speer MC, *et al*. *A* common MUC5B promoter polymorphism and pulmonary fibrosis. N Engl J Med 2011;364:1503–12.
11 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.
12 Karczewski KJ, Francioli LC, Tiao G, *et al*. *The* mutational constraint spectrum quantified from variation in 141,456 humans. Nature 2020;581:434–43.
13 McDermott GC, Doyle TJ, Sparks JA. Interstitial lung disease throughout the rheumatoid arthritis disease course. Curr Opin Rheumatol 2021;33:284–91.
14 Mathai SK, Newton CA, Schwartz DA, *et al*. Pulmonary fibrosis in the era of stratified medicine. Thorax 2016;71:1154–60.
15 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.
16 FinnGen data release 4. Available: https://finngen.gitbook.io/documentation/, https://r4.finngen.fi
17 Kronzer VL, Huang W, Dellaripa PF, *et al*. *Lifest*yle and clinical risk factors for incident rheumatoid arthritis-associated interstitial lung disease. J Rheumatol 2021;48:jrheum.200863:656–63.

Ann Rheum Dis: first published as 10.1136/annrheumdis-2021-220698 on 3 August 2021. Downloaded from http://ard.bmj.com/ on December 14, 2021 at University of Helsinki. Protected by copyright.