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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.

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

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.

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



► <http://dx.doi.org/10.1136/annrheumdis-2021-220698>



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

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 Europeans¹²) 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, $p=3.87 \times 10^{-77}$), and among patients with RA, with a HR of 2.27 (1.75–2.95, $p=8.15 \times 10^{-10}$). 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, $p=4.07 \times 10^{-5}$).

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

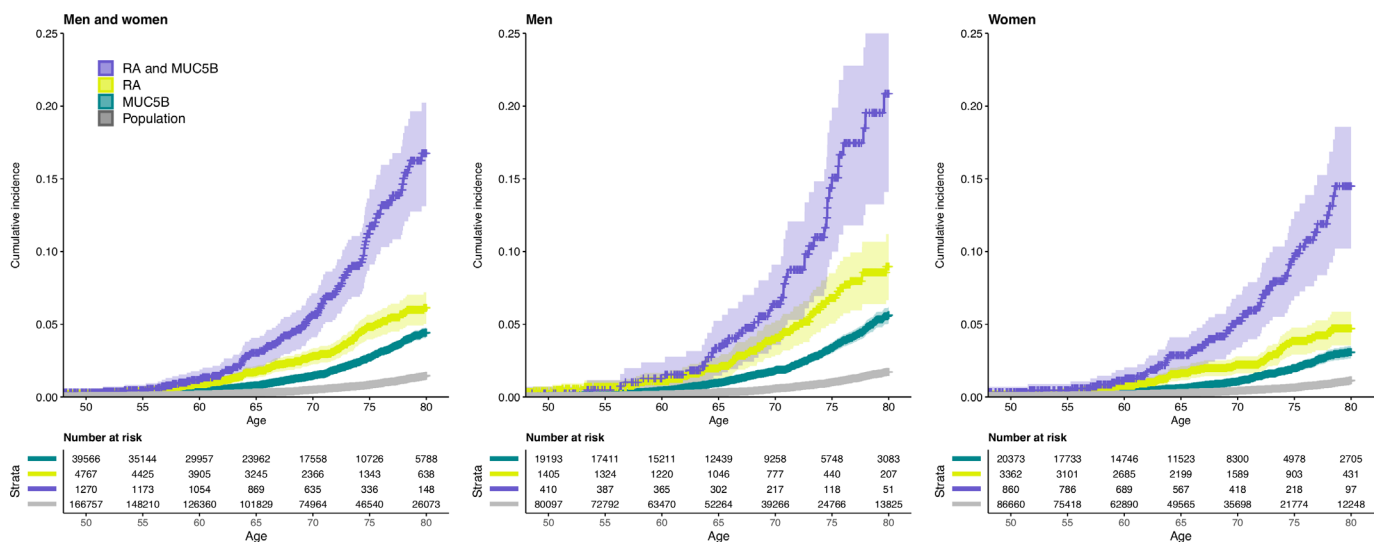


Figure 1 Lifetime risk of interstitial lung disease in the population for *MUC5B* carriers and non-carriers with respect to diagnosis of RA. The risks are shown for men and women both combined and individually. *MUC5B*=carriers of the minor allele for the promoter variant rs35705950. Sample size: 293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

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

	Individuals without RA		Individuals with RA	
	Non-carriers of <i>MUC5B</i> promoter variant	Carriers of <i>MUC5B</i> promoter variant	Non-carriers of <i>MUC5B</i> promoter variant	Carriers of <i>MUC5B</i> 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 IPE.^{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 populations¹¹, 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

¹Centre for Rheumatology and Clinical Immunology, and Department of Medicine, Turku University Hospital and University of Turku, Turku, Finland

²Institute for Molecular Medicine Finland (FIMM), Helsinki Institute of Life Science, University of Helsinki, Helsinki, Finland

³Analytic and Translational Genetics Unit, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA

⁴Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA

⁵Department of Rheumatology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

⁶Orton Orthopaedic Hospital, Helsinki, Finland

⁷Department of Public Health, University of Helsinki, Helsinki, Finland

⁸Department of Mathematics and Statistics, University of Helsinki, Helsinki, Finland

⁹Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA

¹⁰Administration 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.ppsph.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.bbmrifi.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 Isomäki (Pirkanmaa Hospital District, Tampere, Finland); Laura Pirilä (Hospital District of Southwest Finland, Turku, Finland); Olli Kaipainen-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 Lertratnanakul (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); Kirsä Kalpala (Pfizer, New York, NY, United States); Nan Bing (Pfizer, New York, NY, United States); Xinli Hu (Pfizer, New York, NY, United States); Kirsä 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 Palta (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); Tuuliikki 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); Kirsä Auro (GlaxoSmithKline, Brentford, United Kingdom); Caroline Fox (Merck, Kenilworth, NJ, United States); Anders Mälärstig (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 Mälärstig (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'een 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); Valteri Julkunen (Northern Savo Hospital District, Kuopio, Finland); Hilikka 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); Kirsä 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

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); 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 Carpen (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); Saira 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); Andrew 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). Ophthalmology 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); Katarina Hannula-Jouppi (Hospital District of Helsinki and Uusimaa, Helsinki, Finland); Teea Salmi (Pirkanmaa Hospital District, Tampere, Finland); Sirkku Pelttonen (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 Mäkkälä (Hospital District of Southwest Finland, Turku, Finland); Eeva Ekholm (Hospital District of Southwest Finland, Turku, Finland); Marja Väärämäki (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 Esmaeli (Abbvie, Chicago, IL, United States); Slavé Petrovski (Astra Zeneca, Cambridge, United Kingdom); Eleanor 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,

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 Bhargale (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); Jason 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, 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 Jumbulingam (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: Elna 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); Awais 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). Elna 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 Garcia-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

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-Squibb 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 Fingenius® services (<https://site.fingenius.fi/en/>) managed by FINBB. The remaining data are available within the article, supplemental information or available from the authors upon request.

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ORCID iDs

Antti Palomäki <http://orcid.org/0000-0002-8835-8116>

Nina Mars <http://orcid.org/0000-0002-7259-5993>

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Supplementary Table 1. Effect of rheumatoid arthritis (RA) and MUC5B on risk of interstitial lung disease (ILD), accounting for competing risks (non-ILD related death).

	Population	MUC5B	RA	RA and MUC5B
Risk of ILD in men				
Lifetime risk, %	1.5 %	4.8 %	8.5 %	19.5 %
HR (95% CI)	Reference	3.20 (2.84-3.62)	6.00 (4.66-7.73)	11.7 (8.52-16.1)
p-value	-	4.13×10^{-79}	7.21×10^{-44}	1.79×10^{-51}
Risk of ILD in women				
Lifetime risk, %	1.1 %	2.9 %	4.6 %	14.1 %
HR (95% CI)	Reference	2.64 (2.25-3.09)	4.54 (3.57-5.77)	12.6 (9.49-16.7)
p-value	-	1.64×10^{-33}	2.68×10^{-35}	8.91×10^{-70}

Supplementary Table 2. Characteristics of the epidemiological and disease-based cohorts, and hospital biobanks (marked with an asterisk) in the FinnGen dataset used in the study.

	Interstitial lung disease			Rheumatoid arthritis			Mean age at recruitment	Mean age at the end of follow-up or death
	Number of controls	Number of cases	Prevalence	Number of controls	Number of cases	Prevalence		
AURIA BIOBANK*	31371	208	0.66 %	30433	1146	3.63 %	62.8	64.0
BIOBANK OF CENTRAL FINLAND*	7957	54	0.67 %	7547	464	5.79 %	58.6	59.6
BIOBANK OF EASTERN FINLAND*	9798	62	0.63 %	9456	404	4.10 %	62.2	63.1
BLOOD SERVICE BIOBANK	34330	14	0.04 %	34315	29	0.08 %	43.6	44.7
BOREALIS BIOBANK*	8657	96	1.10 %	8372	381	4.35 %	62.6	63.8
HELSINKI BIOBANK*	60819	502	0.82 %	59440	1881	3.07 %	56.9	58.3
TAMPERE BIOBANK*	20147	218	1.07 %	19725	640	3.14 %	56.7	58.1
TERVEYSTALO BIOBANK	6644	11	0.17 %	6498	157	2.36 %	51.0	50.7
THL BIOBANK ATBC	8446	102	1.19 %	8472	76	0.89 %	62.9	77.0
THL BIOBANK BOTNIA	11441	40	0.35 %	11348	133	1.16 %	51.5	68.3
THL BIOBANK COROGENE	4377	69	1.55 %	4346	100	2.25 %	65.8	75.6
THL BIOBANK FINHEALTH 2017	5719	15	0.26 %	5648	86	1.50 %	54.6	57.4
THL BIOBANK FINRISK 1992	4760	32	0.67 %	4685	107	2.23 %	44.2	69.7
THL BIOBANK FINRISK 1997	6799	48	0.70 %	6712	135	1.97 %	48.3	68.9
THL BIOBANK FINRISK 2002	6689	34	0.51 %	6605	118	1.76 %	47.9	64.8
THL BIOBANK FINRISK 2007	4969	27	0.54 %	4896	100	2.00 %	51.2	63.6
THL BIOBANK FINRISK 2012	5093	12	0.24 %	5021	84	1.65 %	51.1	58.8
THL BIOBANK HEALTH 2000	6293	19	0.30 %	6190	122	1.93 %	55.7	72.0
THL BIOBANK HHS	3253	39	1.18 %	3266	26	0.79 %	47.5	79.0
THL BIOBANK MIGRAINE	7700	28	0.36 %	7610	118	1.53 %	44.8	58.6
THL BIOBANK SUPER	8249	16	0.19 %	8222	43	0.52 %	46.9	49.3
THL BIOBANK T1D	9891	28	0.28 %	9701	218	2.20 %	32.7	52.0
THL BIOBANK TWINS	11003	98	0.88 %	10892	209	1.88 %	48.5	68.9
Other	7602	193	2.48 %	7703	92	1.18 %	54.8	58.8

Supplementary Table 3. Diseases excluded from the study. We excluded from all analyses 11,808 individuals without rheumatoid arthritis who had at least one record for any of these diseases.

	Hospital discharge registry			Hospital discharge registry codes to exclude	Cause of death registry			Cause of death registry codes to exclude	Kela* reimbursement codes
	ICD-10	ICD-9	ICD-8	ICD-9	ICD-10	ICD-9	ICD-8	ICD-9	
Systemic lupus erythematosus	M32	7100	7431		M32	7100	7431		
Inflammatory bowel disease									
Crohn disease	K50	555	5630		K50	555	5630		
Ulcerative colitis	K51	556	5631 or 569	5564A	K51	556	5631 or 569	5564A	
IBD patients in Kela*-register									208 or 209
Systemic sclerosis	M34	7101	7340		M34	7101	7340		
Ankylosing spondylitis	M45	7200	7124		M45	7200	7124		
Dermatopolymyositis	M33				M33				
Juvenile dermatomyositis	M330	7103A			M330	7103A			
Other dermatomyositis	M331	7103B	7160		M331	7103B	7160		
Polymyositis	M332	7104	7161		M332	7104	7161		
Dermatopolymyositis, unspecified	M339				M339				
Myositis	M60	7280	732		M60	7280	732		

*KELA = the Social insurance Institute of Finland

Supplementary Methods

Diseases

FinnGen is a collection of prospective epidemiological and disease-based cohorts and hospital biobank samples, aiming for a collection of 500,000 genotype samples from Finnish individuals by 2023. The study uses FinnGen data freeze 7. Further information about the subcohorts included in FinnGen can be found in **Supplementary Table 2**.

Age at RA onset was defined through the first registered diagnosis in the registries (age ≥ 16 at diagnosis accepted as case). Age at ILD diagnosis was defined through the first registered diagnosis in the registries (at death, if death was the only event; age ≥ 16 at diagnosis accepted as case, with 8 individuals excluded due to diagnosis under age 16). 630 individuals were excluded due to no further healthcare contacts with ILD within 5 years after the initial diagnosis (individuals with ILD death as first event considered as cases). Competing risks were defined as any non-ILD related cause of death identified from the registry on causes of death. We excluded from all analyses a further 11,808 individuals without RA who had at least one record for any of the following diseases: systemic lupus erythematosus, inflammatory bowel disease, systemic sclerosis, ankylosing spondylitis, dermatomyositis, or myositis (**Supplementary Table 3**). The full FinnGen Data Freeze 7 consists of 306,418 adults (age ≥ 18), and with the exclusions listed above, the final sample size was 293,972.

Genotyping and imputation

The samples are genotyped with Illumina and Affymetrix arrays (Illumina Inc., San Diego, and Thermo Fisher Scientific, Santa Clara, CA, USA). Individuals with ambiguous gender, high genotype missingness ($>5\%$), excess heterozygosity ($\pm 4SD$) and non-Finnish ancestry were excluded, as well as all variants with high missingness ($>2\%$), low Hardy–Weinberg equilibrium p-value ($<1e-6$) and minor allele count ($MAC < 3$). Array data pre-phasing was carried out with Eagle 2.3.527 with the number of conditioning haplotypes set to 20,000. The genotypes have been imputed with using the SISu v3 population-specific reference panel developed from high-quality data for 3,775 high-coverage (25–30x) whole-genome sequencing in Finns. The detailed genotype imputation workflow can be found at <https://dx.doi.org/10.17504/protocols.io.xbgfijw>. The dataset uses genome build 38 (hg38). Variant extraction from VCF files with PLINK v2.00a2.3LM.45 using `--export A`. The HWE p-value for rs35705950 was 0.18.

Replication in UK Biobank

UK Biobank is a prospective cohort study comprising approximately 500,000 individuals from across the United Kingdom, aged between 40 and 69 at recruitment. The cohort contains deep phenotyping, including biological measurements, lifestyle factors, and blood biomarkers. The dataset has been imputed using the merged UK10K and 1000 Genomes (phase 3) reference panels.¹ Details on the cohort, as well as data generation and imputation have been previously described.² RA was defined as at least two contacts with ICD-10 codes beginning with M05 (seropositive RA) or M06 (seronegative RA) in the inpatient hospital data (data field 41270; age for earliest visit from data field 41280). The sample size in the UK Biobank analysis was 343,676 (White British individuals unrelated based on KING kinship coefficient <0.0442). We identified 1,911 RA cases (1,368 women), with their mean age at RA onset at 58.5 years (s.d. 8.9 years). This analysis was conducted with the UK Biobank Resource under Application Number 22627.

Statistical analysis

With age as time scale, all regression models were stratified by sex, adjusting for ten principal components of ancestry, as well as genotyping array (FinnGen and UK Biobank), cohort (FinnGen), and batch (UK Biobank). The proportional hazards assumption was evaluated by Schoenfeld residuals and log–log inspection. Meta-analysis was performed by inverse-variance weighting. Competing risk models were performed by fitting the Fine and Gray proportional subdistribution hazards regression model using the R package *cmprsk*. Function *crr()* was used for obtaining sex-specific effect sizes with 95% confidence intervals (CIs) with the covariates inputted as a numerical covariate matrix. The lifetime risks were estimated with *cuminc()*, which estimates the cumulative incidence functions from the output generated by *crr()*. All tests were two-tailed.

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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 Kaipainen-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 Tabuena	University of Tampere
Johanna Hiltunen	Hospital District of Helsinki and Uusimaa, Helsinki, Finland
Johanna Palta	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
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 Meg Ehm GlaxoSmithKline, Brentford, United Kingdom
 Kirsi Auro GlaxoSmithKline, Brentford, United Kingdom
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 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 Mälärstig 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
 Hilikka 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 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 R ueger 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 Mets arinne Hospital District of Southwest Finland, Turku, Finland
 Mika K ah onen Pirkanmaa Hospital District, Tampere, Finland
 Juhani Junttila Northern Ostrobothnia Hospital District, Oulu, Finland
 Markku Laakso Northern Savo Hospital District, Kuopio, Finland
 Jussi Pihlajam aki 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, Jyv askyl a, 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 R am o 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
 Saira 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

Ophthalmology 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 Podgoraia 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 Väärasmäki	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, United States
Yunfeng Huang	Biogen, Cambridge, MA, United States
Joseph Maranhville	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 Bhargale	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
Finland Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki,
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 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