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Rheumatoid arthritis

Systematic review and independent validation of genetic factors of radiographic outcome in rheumatoid arthritis identifies a genome-wide association with *CARD9*

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ABSTRACT

Objectives: This study aimed to investigate non-HLA genetic mechanisms underlying radiographic severity in rheumatoid arthritis (RA).
Methods: A systematic review of publications reporting non-HLA genetic associations with radiographic severity in RA across ancestries was undertaken. Experimental validation was performed in the Norfolk Arthritis Register, comprising 1407 patients with available genetic and treatment data followed prospectively for up to 10 years, with 2198 longitudinal radiographs. Genome-wide genotyping was performed with Illumina Human Core Exome Array. Radiographic outcomes (presence of erosions; Larsen score) were modelled longitudinally. Fine mapping and functional annotations to refine associations to potential causative loci were undertaken using FUMA, PolyPhen2, and RegulomeDB.
Results: The systematic review identified 102 publications reporting 139 independent associations with radiographic outcome. Association with 15 independent polymorphisms were replicated in the Norfolk Arthritis Register data set, implicating adaptive immune processes (Th1, Th2, and Th17 pathways), cytokine regulation, and osteoclast differentiation. Notably, we refined the association of rs59902911 at the *CARD9* locus to an intronic polymorphism within an active enhancer (rs78892335), achieving genome-wide significance and with an effect size exceeding the minimal clinically important difference for each copy of the minor allele (4.78

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Larsen units/copy; 95% CI, 3.15-6.41; p = 9.01×10^{-9}). This polymorphism is associated with the expression of *CARD9* in immune cells, including B cells.
Conclusions: We provide a comprehensive list of validated genetic associations with RA outcome and demonstrate that non-*HLA* polymorphisms can associate with radiographic severity independently of disease susceptibility. This highlights the importance of dedicated genetic outcome studies for patient stratification in precision medicine for RA.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- The genetic architecture of prognosis and outcomes in immune-mediated diseases remains poorly understood compared to that of susceptibility.

WHAT THIS STUDY ADDS

- We provide an extensive review of the literature on genetic associations with radiographic severity in rheumatoid arthritis (RA) summarising key findings including cohort details, effect sizes, and study designs, generating an important resource for future research.
- rs78892335 located within the *ENTR1* gene, is associated with radiographic outcome, reaching genome-wide significance. This single-nucleotide polymorphism regulates expression of *CARD9,* which plays a role in inflammatory cytokine production, and suggests pathways that could be key drivers of RA severity and a target for future therapies.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

- Genetic drivers of prognosis in RA can differ from those influencing disease susceptibility, particularly in non-HLA loci. Our findings emphasise the need to study RA progression pathways independently of susceptibility mechanisms.

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disorder characterised by flares of inflammation of synovial joints. This leads to pain and swelling and, if left uncontrolled, can result in permanent disability. Determinants of prognosis in RA and other immune-mediated diseases remain poorly understood.

In RA, patients may develop radiographic damage comprises characteristic erosive changes, periarticular osteopenia, and loss of joint space [1]. Some individuals exhibit a particularly aggressive, erosive phenotype [2]. There are some established predictors of radiographic severity, for example, anticyclic citrullinated peptide (anti-CCP) positivity [3]. Radiographic damage is the result of the cumulative burden of uncontrolled inflammation. However, only 32% of the total variance of joint destruction has been attributed to known risk factors, which is not enough in isolation to sufficiently predict clinical course [4] The genetic contribution to joint destruction likely accounts for some of this with heritability estimates of ~50% [5].

Genome-wide association studies (GWAS) have focussed on identifying susceptibility markers, leaving the genetic architecture of prognosis relatively understudied. Approximately 150 loci have been associated with susceptibility to RA, with the *HLA* region accounting for the largest effect sizes [6–8]. In contrast, identification of robust genetic markers of prognosis has been hampered by several, significant challenges. These include confounders such as treatments, as well as lack of large, well-characterised cohorts with sufficient follow-up data available.

Despite these challenges, it is clear that at least some genetic mechanisms involved in susceptibility to RA, unsurprisingly, overlap with those involved in disease severity. In particular, HLA-DRB1 haplotypes as defined by amino acids at positions 11/13, 71, and 74 have been associated with susceptibility and radiographic severity, as well as all-cause and cardiovascular disease–related mortality [2,9]. Outside the HLA region, results are much more conflicting. Although there is a large body of literature reporting potential non-*HLA* associations with radiographic severity, most have been identified in small studies and have shown inconsistent results across cohorts, with small effect sizes. Only a minority have been replicated, including single-nucleotide polymorphisms (SNPs) near the *TRAF1* gene, a known susceptibility locus [10].

It is beginning to emerge that some loci which are associated with prognosis, are not associated with susceptibility [6]. A notable example is an SNP in the *FOXO3A* gene, where the minor allele of rs12212067 has been associated with lower radiographic severity of RA and lower severity of Crohn disease, but this locus is not associated with disease susceptibility for either condition [6,11] The minor allele is associated with reduced inflammatory response secondary to increased monocyte production of interleukin (IL)-10 and reduced production of tumour necrosis factor (TNF) [6,11,12]. This implies that specific genetic factors, although not involved in the initiation of the disease process, could be involved in potentiation and maintenance of the inflammatory response once it has begun and has been noted in other complex diseases, such as multiple sclerosis [13].

In this study, we aimed to explore genetic mechanisms driving radiographic severity in RA, moving beyond the well-established association with the *HLA* region. By reviewing the existing literature and using a large, well-characterised inception cohort of patients, our goal was to identify non-*HLA* loci that warrant prioritisation for future research and clinical application.

PATIENTS AND METHODS

Identification of SNPs

A systematic literature review was performed by 1 reviewer (SDS) according to the updated PRISMA 2020 guideline [14] to identify all SNPs that have previously been reported to associate with radiographic outcome in RA ($P < .05$), including reports until November 12, 2022. A PRISMA checklist is available as a Supplementary File. Methods of evaluation are included in Supplementary Methods including search strategy, PICOS (population, intervention, comparison, outcome, and study design) criteria and inclusion/exclusion criteria (Supplementary Tables S1-S3). Relevant information from each study was extracted (Supplementary File S2, Tab 1).

Patients and cohorts

The Norfolk Arthritis Register (NOAR) is an inception cohort of patients with inflammatory polyarthritis (IP) recruited since 1989 and followed prospectively for up to 20 years. IP was defined as the presence of 2 or more swollen joints for a

minimum of 4 weeks duration. The majority of patients (84%) were recruited within 2 years of disease onset. Patients with disease duration of over 5 years at time of registration were excluded. All patients were recruited after informed consent. Ethical approval was granted by the Norwich Research Committee (NOAR – REC Ref 2003/075, December 18, 2003, Norwich Local Research Committee [NHS]).

A case note review of patients in the NOAR cohort was undertaken, during which the subsequent clinical diagnosis made by a consultant rheumatologist at the last available follow-up was recorded. As the target population for the study was RA, patients with other confirmed diagnoses were excluded (n = 159). A flowchart of patients illustrating patients retained for final analysis is depicted in Supplementary Figure S1.

Radiographic outcome

During the first 10 years of follow up, radiographs of hands and feet were performed at regular intervals. Each radiograph was scored using the method by Larsen et al [15], a validated tool to determine radiographic severity of RA. In brief, a score from 0 to 5 is attributed to each small joint of the hands or feet, where 0 signifies no joint damage and 5 is complete destruction of the joint. A 2.0-mm or larger cortical break was labelled as an erosion and was assigned a score of 2 or greater. The sum of scores for each individual joint represents a score per patient radiograph, ranging from a Larsen score of 0 to 200. Each radiograph was scored in this way by 2 medically qualified staff, with a third investigator arbitrating in cases of disagreement.

Genotyping, quality control, and imputation

Patients from the NOAR cohort with available DNA and one set of hands and feet X-rays available at least at one follow-up time point were genotyped in 3 independent batches. Further details are available in Supplementary Methods.

Statistical analysis

Radiographs were not performed systematically at every time point. Therefore, longitudinal models were used. Analysis was performed consistent with and published technical details [2].

Analysis was carried out on the cohort with genetic, treatment, and radiographic data available. *LDlink* (National Institutes of Health; https://ldlink.nih.gov/; the CEU European reference panel) was used to determine the linkage disequilibrium (LD) between chromosome 6 SNPs and rs660895, a SNP tagging HLA alleles associated with RA susceptibility and severity [16]. Those SNPs with evidence of LD (R^2 or D' > 0.4) with HLA susceptibility alleles were excluded from further analysis (Supplementary Table S1). SNPs were all tested for association with presence of erosions of the hands and feet as a binary variable using a generalised estimating equation model with logit-link function and an exchangeable within-subject correlation structure. We report results as odds ratios (ORs) with 95% confidence intervals (CIs).

Subsequently, association of SNPs with Larsen score was tested as a longitudinal variable. As this variable was nonnormally distributed, statistical association testing was performed by fitting a generalised linear latent and mixed model (GLLAMM) with discrete random effects and 3 latent classes [2,11]. Results are reported as β coefficients (representing change in Larsen score for every copy of the minor allele), with 95% CIs.

All generalised estimating equation and GLLAMM models were adjusted for age of onset, disease duration and the square of disease duration to model the nonlinear progression of radiographic damage over time in NOAR. Disease duration was calculated for each radiograph and each patient as the sum of disease duration at the time of recruitment plus the duration of follow up at the time of the radiograph. GLLAMM models were additionally adjusted for square of age of onset. The rationale for appropriateness of fitting a quadratic term in this cohort has previously been described [2]. All models were tested under an additive genetic model (SNPs coded as 0, 1 and 2 for the number of copies of the minor allele carried by each patient). Each individual treatment at recruitment and at every follow up, even when no radiographs were taken, has been recorded for each patient. A categorical dummy variable (presence/absence) of treatment with a corticosteroid was created, alongside an independent categorical variable for treatment with any disease-modifying antirheumatic drug (DMARD), for every follow up time point. Consequently, these variables capture the on/off effect of treatment longitudinally. All longitudinal models were adjusted for these 2 time-varying covariates to remove the effect of cumulative exposure to DMARD and corticosteroid treatments to time of radiograph.

Because this study was designed to replicate previously reported associations, 1-sided *P* values are presented, as we specifically tested for effects in the same direction as reported. Results are reported without correction for multiple testing. The Benjamini–Hochberg false discovery rate at 0.05 was applied to correct for multiple comparisons, and associations that remained significant after this adjustment are highlighted.

Other analysis

As many studies in the literature have previously used a dominant genetic model, results using this model are also reported in Supplementary File S2. Stratified analysis was performed by anti-CCP status, and this is reported alongside analysis of the whole cohort (Supplementary File S2, Tabs 2 and 3). Models adjusted for anti-CCP status are presented in Supplementary File S2, Tabs 4 and 5; association testing restricted to patients who met the ACR 1987 criteria in Supplementary File S2, Tabs 6 and 7; and those who met the ACR 2010 criteria in Supplementary File S2, Tabs 8 and 9. Mediation analysis was performed to determine the effect of anti-CCP status for SNPs associated with radiographic severity (Supplementary File S2, Tab 10).

Fine mapping analysis and functional annotation

For SNPs nominally associated in the NOAR data set ($P < .025$), association with radiographic severity with all SNPs within a 500-kb window of each of these SNPs was tested, and 95% credible single-nucleotide polymorphism sets (CSSs) were determined [17]. CSSs use a Bayesian approach to prioritise likely causative SNPs through assignment of probability, based on statistical evidence and LD. Plots of *P* values (2-sided) for regions of interests were generated in R using package *LocusZoomR* [18,19].

FUMA was used as a basis for functional mapping and annotation in order to explore the functional impact of potential causative genetic loci implicated in radiographic severity [20]. FUMA combines data from databases such as CADD (combined annotation–dependent deletion) alongside plots to identify likely causal SNPs. A high CADD score indicates a variant is

likely to have significant functional impact, based on integrated data from multiple sources such as evolutionary conservation, protein structure and gene regulation. Scores range from 1 to 99. RegulomeDB scores were obtained from the website. RegulomeDB provides information on the likelihood of a variant to affect gene regulation, where a higher score suggests a lower likelihood of regulatory impact [21–23]. Scores range from 1 (highly likely to have functional impact) to 7 (least likelihood of functional impact). Open Targets Genetics was also used to prioritise variants based on published information such as gene expression data [24]. Likely functional consequences of exonic SNPs were predicted using PolyPhen2 [25] and SIFT [26].

Gene ontology pathway analysis

Gene ontology (GO) pathway analysis was used to identify pathways enriched for genes associated with radiographic outcome in NOAR [27].

RESULTS

Literature review of previous non-HLA associations with radiographic severity

In total, 1162 records were identified from Medline and screened for eligibility. Figure 1 is a flowchart that summarises reasons for exclusion at each stage. A total of 102 articles fulfilled the inclusion criteria.

Figure 2

We identified 139 independent SNPs (European ancestry LD < 0.8) associated with radiographic outcome in RA from the literature (Table 1) [28–126]. Ancestry of the cohort is shown alongside the radiographic outcome used in the study (Supplementary File S2, Tab 1). Further information extracted from each individual article is shown in Supplementary File S2, Tab 1. Two TNF SNPs (rs1800629 and rs361525) were excluded from further analysis due to LD with the HLA (Supplementary Table S4) [127].

Cohort characteristics

Experimental validation was performed in the NOAR cohort (clinical characteristics in Table 2). There was 1407 patients with IP with at least 1 radiograph, genetic, and treatment data available. NOAR is an inception cohort; patients included in this study were recruited early in their disease course between 1989 and 2008. The majority of patients were not treated with any DMARD, and <4% were on biologic drug treatment.

In total, 144 SNPs were identified, 139 of which were independent (LD < 0.8). Gene names are those referenced in the original publication, which in most cases represents closest gene. For further information please, see Supplementary File S1, Tab 1. This includes information on the following: title, year, authors, journal, URL, ancestry, whether known susceptibility locus, chromosomal position, minor and major alleles and frequency in both NOAR cohort and in Europeans (dbVar), gene model used in original publication, sample size, radiographic outcome used, direction of effect, effect sizes, and cohort characteristics from original publication (percentage rheumatoid factor positive, anti-CCP positive, female, and mean age).

Associations with radiographic outcome

Of the 139 SNPs identified from the systematic review, 130 could be tested in NOAR (9 were not available in the imputed data set). Effect sizes for presence of erosions and Larsen score were heavily correlated ($P = 2.22 \times 10^{-16}$) (Supplementary Figure S18). There were 15 independent SNPs (~12%), which reached a P value of <.05, including 4 SNPs with $P < .005$ (Table 3). Of the 15 SNPs, 14 are not located in known susceptibility regions. One SNP (rs59902911) located in exon 5 of *CARD9* retained statistical significance following correction for multiple testing. The minor allele (minor allele frequency [MAF] = 0.03) was associated with increased risk of erosions (OR, 1.66; 95% CI, 1.05-2.62; $P = 1.51 \times 10^{-2}$) and with increased Larsen score ($\beta = 4.65$; 95% CI, 2.87-6.42; $P = 1.46 \times 10^{-7}$). This effect size is equivalent to approximately

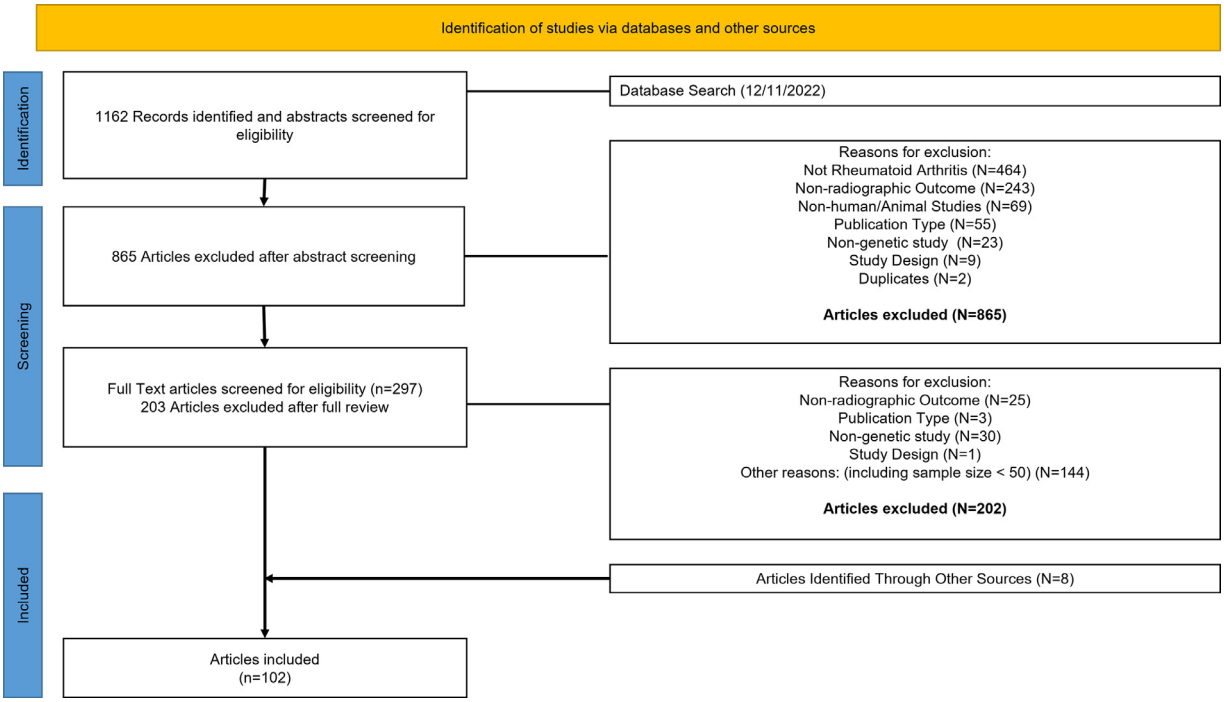

Figure 1. Flowchart of literature review, depicting literature review and reasons for exclusion.

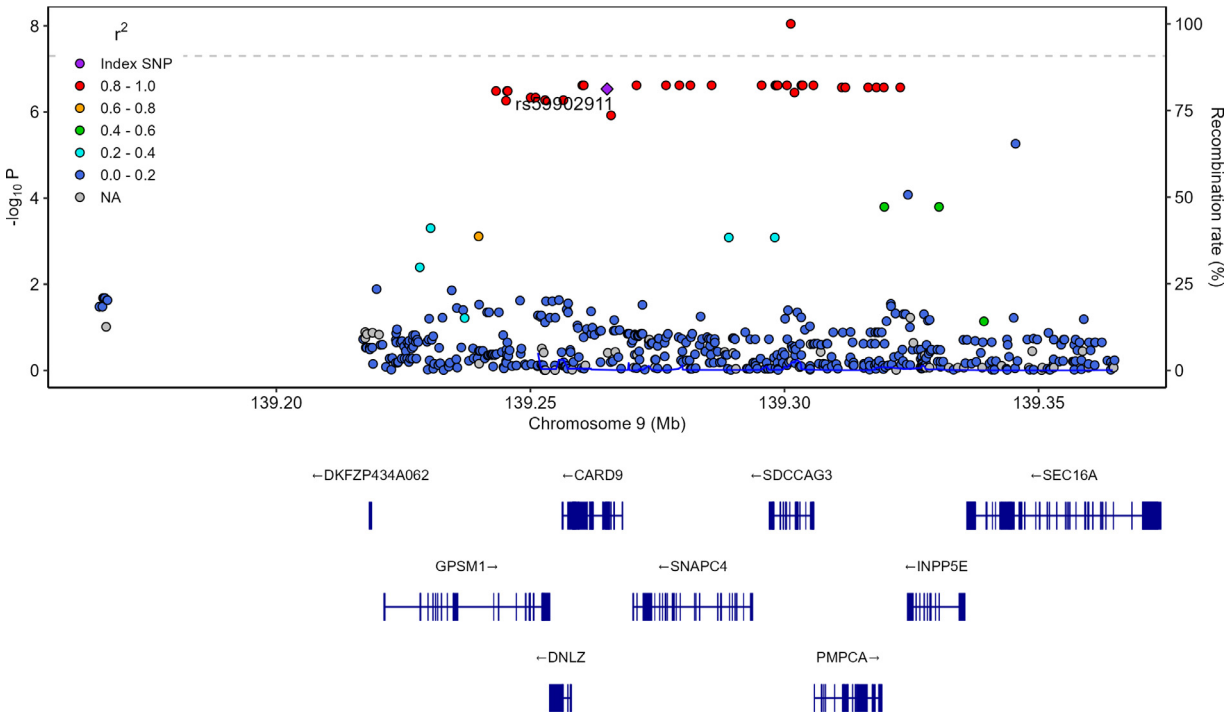

Figure 2. Fine mapping of association with radiographic outcome at the *CARD9* locus, with a LocusZoom plot generated using the LocusZoomR [18,19]. The index SNP, rs59902911, is highlighted in purple. The dotted line refers to genome-wide significance. Each dot represents a SNP, colour-coded for the linkage disequilibrium to the index SNP, and y axis represents the absolute value of the $\log_{10}$ of the *P* value for the association with Larsen score. Chromosomal positions are presented on the x axis, with the genetic structure of the region (genes, exons, introns, direction of transcription, and gene names). Note *ENTR1* gene is also known as *SDCCAG3*.

twice the minimal clinically important difference (2.3 units) for each copy of the minor allele [15]. Table 3 shows association results in NOAR for 13 additional SNPs from Table 1, which were previously replicated in at least 2 independent cohorts and were reported in 2 independent publications. These SNPs did not formally reach the threshold for significance in this study in NOAR.

Effect of anti-CCP-status on non-HLA associations with radiographic outcome

Genetic mechanisms underlying RA severity may differ by anti-CCP status. To explore this, stratified analyses were conducted by anti-CCP status (Supplementary File S2, Tabs 2 and 3). Additionally, some SNPs may influence severity indirectly by increasing the likelihood of anti-CCP positivity. Recognising this distinction is crucial for understanding the mechanisms driving these associations and assessing their clinical relevance. To address this, subanalysis was performed with adjustment for anti-CCP status. (Supplementary File S2, Tabs 4 and 5).

For SNPs associated with radiographic severity in the overall cohort (Table 3), mediation analysis (Supplementary File S2, Tab 10) was performed to determine whether these effects were independent of anti-CCP status. One SNP, rs10760130 (*TRAF1*), was associated with anti-CCP positivity, and the association with radiographic severity disappeared after adjusting for anti-CCP status. This suggests that this SNP may influence radiographic severity primarily through their effect on anti-CCP positivity.

Of those associated with radiographic severity in overall cohort, 2 SNPs – rs6887695 (*IL12β*) and rs59902911 (*CARD9*) – showed greater effect sizes in anti-CCP–positive patients. However, CIs between anti-CCP–positive and anti-CCP–negative patients overlapped for rs6887695. In the case of rs59902911, the minor allele (T) of rs59902911 was significantly associated with higher Larsen scores in anti-CCP–positive patients (7.94; 95% CI, 4.00-11.88; $P = 3.9 \times 10^{-5}$) but showed no significant association in anti-CCP–negative patients (1.21; 95% CI, −0.77 to 3.20; $P = 0.12$). This suggests that this SNP may exert a more pronounced effect on radiographic severity in the context of anti-CCP–related mechanisms, potentially interacting with pathways specific to anti-CCP–positive RA.

Fine mapping analysis

For radiographic severity SNPs previously identified in the literature, which replicated in NOAR (Table 3), fine mapping analysis was performed to identify potential causal SNPs within the genomic vicinity (for those SNPs $P < .025$ in NOAR). Visual results are depicted using LocusZoom plots (Figure 2 and Supplementary Figures S2-S12).

CSS analysis was used to prioritise likely causative SNPs. For the majority of 10 regions explored, CSSs were broad, which is reflective of small effect sizes in outcome studies. However, for rs1805011 (*IL4R*) and rs506746 (*NALCN/ITGBL1*), the CSSs were unusually small containing only 1 SNP and 3 SNPs, respectively. These SNPs were, however, in low LD to rs1805011 ($R^2 = 0.0003$) and rs506746 ($R^2 = 0.0001$). The absence of these candidate SNPs from the 95% CSS suggests limited evidence supporting their direct causal role within this analysis framework.

Based on the results of their statistical associations, LD patterns, and potential functional relevance, FUMA analysis was applied to rs2243250 (*IL4*), rs6887695 (*IL12B*), and rs59902911 (*CARD9*). Results are shown in Supplementary File S2, Tabs 11-13, respectively. LocusZoom plots representing SNPs within a 500-kb window or an LD window ($R^2 > 0.6$),

Table 1
A summary of published genetic associations with radiographic outcome in RA identified from literature review (until November 2022)

CHR	Gene	SNP	Reference
1	*FCGR2B*	rs1050501	[28,29]
1	*CRP*	rs2808630	[30]
1	*Cyclooxygenase-2*	rs20417	[31]
1	*FCRL3*	rs7528684	[32–35]
1	*PARP1*	rs1805413	[36]
1	*IL10*	rs1800872	[37]
1	*IL10*	rs1800896	[37–39]
1	*FcγR3A*	rs396991	[40–42]
1	*IL10*	rs6703630	[43]
1	*IL6R*	rs4845374	[44]
1	*IL6R*	rs4845618	[44]
1	*KIAA1107/C1orf146*	rs80105455	[45]
1	*PADI2*	rs1005753	[46]
1	*PADI4*	rs1748033	[47]
1	*PADI4*	rs2240340	[48,49]
1	*PCSK9*	rs644000	[45]
1	*PTPN22*	rs2476601	[10,37,50,51]
1	*TNFRSF9*	rs228702	[52]
2	*AFF3*	rs11676922	[53]
2	*CTLA4*	rs73055463	[52]
2	*CYP1B1*	rs10012	[40]
2	*IL1A*	rs3783550	[54]
2	*IL1B*	rs1143634	[55]
2	*IL1B*	rs16944	[56]
2	*IL-1 RN*	rs419598	[57,58]
2	*RASGRP3*	rs13014054	[52]
2	*STAT4*	rs7574865	[59,60]
2	*SPAG16*	rs7607479	[61]
3	*CCR5*	rs1799987	[62]
3	*GHRL*	rs696217	[63]
3	*OGG1*	rs3219008	[64,65]
4	*HMGB1P28/TMEM33*	rs7655001	[45]
4	*IL15*	rs4371699/rs6821171/ rs7665842/rs7667746	[66]
4	*SPP1*	rs4754/rs9138	[67]
4	*TLR10*	rs11466657	[68]
5	*C5orf30*	rs26232	[69]
5	*CAPSL*	rs13157282/rs7445819	[45]
5	*IL-12B*	rs6887695	[70]
5	*IL13*	rs1800925	[71]
5	*IL4R*	rs2243250	[72]
5	*LOC100132524/RAI14*	rs10043548/rs10058554	[45]
5	*MiRNA-146a*	rs2910164	[73]
5	*PTGER*	rs6896969/rs76523431	[74]
5	*SLC22A4*	rs2073838	[75]
6	*6q23*	rs13207033	[76]
6	*CDKAL1*	rs981042	[45]
6	*ESR1*	rs1801132	[40]
6	*TNFAIP3-OLIG3*	rs675520	[77]
6	*FOXO3*	rs12212067	[11,12,78]
6	*IL17*	rs3804513	[79]
6	*MnSOD*	rs4880	[80]
6	*PSORS1C1*	rs2233945	[81]
6	*TAGAP*	rs394581	[10]
6	*THEMIS/PTPRK*	rs77843069	[45]
6	*TNF*	rs1800610	[82]
6	*TNF*	rs1800629	[83–88]
6	*TNF*	rs361525	[89]
6	*TNFAIP3*	rs6920220	[90]
6	*TNFAIP3*	rs9376293	[91]
7	*CDK6*	rs42041	[92]
7	*CYP3A4*	rs2740574	[40]
7	*IL6*	rs1800795	[37,93]
7	*IRF5*	rs2004640	[94]
8	*BLK*	rs13277113	[53]
8	*OPG*	rs1485305	[95]
9	*CARD9*	rs59902911	[45]
9	*MOB3B*	rs774351	[45]
9	*TRAF1-C5*	rs7034499	[52]
9	*TRAF1*	rs10760130	[96]
9	*TRAF1*	rs10818488[a]	[60,97]
9	*TRAF1*	rs2900180	[10,96,98]
10	*CYP2C9*	rs1057910/rs1799853	[40]
10	*DKK1*	rs10762715/rs1194750/ rs1441124/rs1528873/ rs1896367/rs1896368	[99]
10	*DKK1*	rs1896367	[99,100]
10	*IL2RA*	rs2104286	[53]
10	*IL2RA*	rs7077067/rs2104286	[52]
10	*MBL*	rs1800450	[101]
10	*SDF-1*	rs1801157	[102]
11	*MMP3*	rs3025082	[103]
11	*ETS1*	rs4362159/rs7108537	[52]
11	*IL18*	rs1946518	[104]
11	*LRP5*	rs3736228/rs2306862/ rs4988321	[105]
11	*MMP12*	rs2276109	[106]
11	*MMP13*	rs2252070	[106]
11	*MMP7*	rs11568818	[106]
11	*TMEM80*	rs7101785[b]	[52]
12	*KIF5A*	rs775241	[10]
12	*NK10*	rs2617169	[107]
12	*NK9*	rs2246809[c]	[107]
13	*NALCN/ITGBL1*	rs506746	[52]
13	*RANKL*	rs2277438	[79,108]
14	*ESR2*	rs1271572	[40]
14	*Granzyme B*	rs12433772/rs8192916	[109]
14	*RAD51B*	rs911263	[110]
14	*ZFP36L1 / C14orf181*	rs189866/rs451066[d]	[111]
16	*IL4R*	rs1805010	[112–114]
16	*IL4R*	rs1119132/rs1801275	[115]
16	*IL4R*	rs1805011/rs1805015/ rs4787423/rs6498016/ rs7191188	[114]
17	*LGALS9*	rs3763959	[116]
17	*MAP3K14*	rs7216796	[45]
17	*p53*	rs1042522	[117]
17	*SHGB*	rs6259	[40]
17	*SOST*	rs4792909/rs6503475	[99]
18	*PTPN2*	rs2542151	[81]
19	*TGF-β1*	rs1982073	[118–120]
19	*LILRA3*	rs103294	[121]
19	*TGF-β1*	rs1800469	[122]
19	*XRCC1*	rs25487/rs25489	[64]
20	*CD40*	rs4810485	[92]
20	*DNMT3B*	rs6087990	[123]
20	*MiRNA-499*	rs3746444	[47]
20	*MMP9*	rs11908352	[111]
21	*HLCS*	rs6517385	[45]
21	*HUNK/SCAF4*	rs2833522	[124]
22	*MIF*	rs755622	[125]
22	*NF2*	rs2158619	[45]
22	*NIPSNAP1*	rs62227968[e]	[45]
X	*IRAK*	rs1059703	[126]

CHR, chromosome; LD, linkage disequilibrium; SNP, single-nucleotide polymorphism.
[a] Variant in LD with rs10760130 (R^2 = 0.972).
[b] Variant in LD with rs4362159 (R^2 = 0.9902).
[c] Variant in LD with rs2617169 (R^2 = 1.0).
[d] Variant in LD with rs189866 (R^2 = 1.0).
[e] Variant in LD with rs2158619 (R^2 = 0.8574).

alongside CADD scores/RegulomeDB scores, are shown in Supplementary Figures S13 to S17.

In the region of rs2243250 (*IL4*), 623 SNPs were in the 95% CSS with 35 in LD (R^2 > 0.7) with rs2243250 (Supplementary File S2, Tab 11) These SNPs spanned the *IL4-KIF3A* region. One SNP was exonic (*KIF3A)* but functional prediction by SIFT suggested this is well tolerated. Many SNPs in this region [20] have strong evidence for involvement in regulatory function (RegulomeDB scores 1a-1f).

Table 2
Cohort characteristics for the Norfolk Arthritis Register (NOAR)

	Total	Baseline[a]	Year 1[b]	Year 2	Year 5	Year 10
No. of patients with available genotype, radiographic outcome, and recorded treatment	1407[c]	415	802	252	550	144
Total No. of radiographs included in the study	2198					
Recruitment period	From 1989 to 2008					
Satisfy 1987 ACR criteria for RA during follow up, n/N (%)	1044/1407 (74)					
Satisfy 2010 ACR criteria for RA during follow up, n/N (%)	1112/1407 (79)					
Sex (male/female), n (%)	455/952 (32/68)					
Age at disease onset (y), median (IQR), % missing	56 (45;66), 0					
Disease duration at baseline (mo), median (IQR), % missing	6.2 (3.0;12.3), 0[d]					
Ever tested positive (anti-CCP), n/N (%)	495/1311 (38)					
Ever tested positive (RF), n/N (%)	740/1402 (53)					
Erosive disease, n/N (%)[e]		203/415 (49)	351/811 (43)	88/263 (34)	241/550 (44)	136/146 (93)
Larsen score, median (IQR)[f]		4 (0-15)	4 (0-14)	2 (0-14)	5 (0-22)	36.5 (17-60)
Treatment, n/N (%)						
On steroids		158/1407 (11)	197/1325 (15)	147/1132 (13)	136/1077 (13)	71/632 (11)
On any DMARD or biologic treatment (excluding steroids)		447/1407 (32)	644/1325 (49)	564/1132 (50)	522/1077 (49)	300/632 (47)
Breakdown (DMARD or biologics)[g], n/N (%)						
Methotrexate		229/1407 (16)	359/1325 (27)	317/1132 (28)	332/1077 (31)	193/632 (31)
Sulphasalazine		188/1407 (13)	247/1325 (19)	210/1132 (19)	160/1077 (15)	87/632 (14)
Chloroquine/hydroxychloroquine		29/1407 (2)	62/1325 (5)	67/1132 (6)	77/1077 (7)	48/632 (8)
Intramuscular gold		9/1407 (1)	20/1325 (2)	19/1132 (2)	10/1077 (1)	6/632 (1)
Cyclosporine		3/1407 (0)	7/1325 (1)	5/1132 (0)	10/1077 (1)	6/632 (1)
Penicillamine		3/1407 (0)	3/1325 (0)	4/1132 (0)	5/1077 (0)	2/632 (0)
Azathioprine		2/1407 (0)	3/1325 (0)	5/1132 (0)	5/1077 (0)	4/632 (1)
Etanercept		2/1407 (0)	6/1325 (0)	11/1132 (1)	14/1077 (1)	9/632 (1)
Auranofin		1/1407 (0)	1/1325 (0)	1/1132 (0)	0/1077 (0)	0/632 (0)
Adalimumab		1/1407 (0)	2/1325 (0)	9/1132 (1)	14/1077 (1)	12/632 (2)
Cyclophosphamide		0/1407 (0)	0/1325 (0)	0/1132 (0)	0/1077 (0)	0/632 (0)
Leflunomide		0/1407 (0)	6/1325 (0)	9/1132 (1)	16/1077 (1)	16/632 (3)
Mycophenolate mofetil		0/1407 (0)	0/1325 (0)	0/1132 (0)	0/1077 (0)	0/632 (0)
Anakinra		0/1407 (0)	0/1325 (0)	0/1132 (0)	0/1077 (0)	0/632 (0)
Infliximab		0/1407 (0)	1/1325 (0)	3/1132 (0)	4/1077 (0)	7/632 (1)
Rituximab		0/1407 (0)	0/1325 (0)	0/1132 (0)	2/1077 (0)	2/632 (0)
Other biologic drugs		0/1407 (0)	0/1325 (0)	0/1132 (0)	0/1077 (0)	3/632 (0)
Other (including drug trials)		2/1407 (0)	5/1325 (0)	6/1132 (1)	3/1077 (0)	1/632 (0)

ACR, American College of Rheumatology; DMARD, disease-modifying antirheumatic drug; RA, rheumatoid arthritis; RF, rheumatoid factor.
[a] At recruitment.
[b] This table shows selected time points. Patients were followed up every year during the first 5 y, and every 2 y between year 5 and 10.
[c] At least at 1 time point with available radiographs and 1 time point with available treatment information during the first 10 y of follow-up. N over follow-ups do not add up to 1407, as not all patients had a radiographic assessment at the same time.
[d] 22 patients of 1407 presented in this table had a disease duration of >5 y at recruitment and were excluded from the genetic association study.
[e] Erosive disease was defined by the presence of at least 1 erosive joint (Larsen score ≥2; cortical break >2.0 mm).
[f] Larsen score ranges from 0 to 200 where higher scores indicate a greater degree of joint damage [15].
[g] Sorted by frequency at baseline.

LocusZoom (Supplementary Figure S5) showed potentially 2 distinct LD blocks associated with Larsen score in the region of rs6887695 (IL12β); 862 SNPs were identified in the 95% CSS. Seventeen SNPs that were in LD ($R^2 > 0.6$) with rs6887695 and, in the second LD block, 37 SNPs, with LD ($R^2 > 0.6$), were given in reference to rs55840985. There were no exonic SNPs in either block. In the first LD block containing rs6887695, 6 SNPs have RegulomeDB scores (1a-1f), suggesting high likelihood of involvement in regulatory function, and 5 SNPs were GWAS hits for susceptibility to number of autoimmune diseases including psoriasis, Takayasu arteritis, and inflammatory bowel disease.

Rs59902911, CARD9 region

Rs59902911 had 30 SNPs in the 95% CSS (Supplementary File S2, Tab 13) and the lead variant rs78892335 (R^2 = .903 with the index SNP rs59902911) reached genome-wide significance for its association with Larsen score (β = 4.78; 95% CI, 3.15-6.41; $P = 9.01 \times 10^{-9}$) (Supplementary File S2, Tab 13). This SNP was not directly genotyped, MAF was 3.4%, and only 1 patient was homozygous for the minor allele (AA). However, it imputed well (R^2 = 0.949), and there was low missingness in the data set (average call rate, 0.998), increasing confidence that this association was not the result of a technical artefact. Figure 3 shows the median Larsen score by genotype over follow-up (years). This intronic SNP is located within the *ENTR1* (also known as *SDCCAG3*) gene in an active enhancer and promotor region in B lymphocytes (RegulomeDB) [22]. Open Targets Genetics show this SNP is an expression quantitative trait loci for CARD9 (minor allele increases expression) in B cells ($P = 2.8 \times 10^{-9}$) [128], $CD4^+$ T cells ($P = 1.7 \times 10^{-60}$) [129], $CD8^+$ T cells ($P = 3.3 \times 10^{-54}$) [129], monocytes ($P = 5.5 \times 10^{-65}$) [130] and neutrophils ($P = 1.5 \times 10^{-13}$) [131–133]. Figure 4 illustrates how this SNP may be implicated in RA prognosis [134,135].

There were 6 exonic SNPs within >0.6 LD of rs59902911, 3 of which were nonsynonymous (Table 4). One of these SNPs

Table 3
List of validated genetic associations with radiographic severity in rheumatoid arthritis

Chr	Position	Gene	SNP (rsID)	A1	A2	MAF	Erosions	Larsen score		
							OR (95% CI)	*P*	*β* coefficient (95% CI)	*P*
Previous non-HLA associations replicated in NOAR[a]										
2	113129630	*IL1RN*	rs419598[b]	C	T	0.27	0.99 (0.84, 1.17)	$4.63 \times e^{-1}$	**−0.64 (−1.32, 0.04)**[c]	$\mathbf{3.32 \times e^{-2}}$
4	141776015	*IL15*	rs6821171	G	T	0.27	**0.86 (0.73, 1.02)**[c]	$\mathbf{4.42 \times e^{-2}}$	−0.03 (−0.76, 0.71)	$4.73 \times e^{-1}$
5	114305447	*KCNN2*	rs11958855	A	G	0.23	1.12 (0.94, 1.34)	$1.03 \times e^{-1}$	**1.14 (0.38, 1.90)**	$\mathbf{1.50 \times e^{-3}}$
5	132673462	*IL4*	rs2243250	T	C	0.13	**1.42 (1.14, 1.78)**	$\mathbf{1.01 \times e^{-3}}$	**1.24 (0.32, 2.17)**	$\mathbf{4.26 \times e^{-3}}$
5	159395637	*IL12B*	rs6887695	C	G	0.32	0.97 (0.82, 1.14)	$3.45 \times e^{-1}$	**−0.72 (−1.37, −0.07)**	$\mathbf{1.48 \times e^{-2}}$
6	159061489	*FCGR3A*	rs394581[d]	C	T	0.28	1.11(0.93, 1.31)	$1.21 \times e^{-1}$	**0.65 (−0.03, 1.32)**[c]	$\mathbf{2.98 \times e^{-2}}$
6	108659993	*FOXO3*	rs12212067[d]	G	T	0.09	**0.78 (0.61, 1.01)**[c]	$\mathbf{2.94 \times e^{-2}}$	−0.70 (−1.80, 0.40)	$1.06 \times e^{-1}$
6	159692840	*SOD2*	rs4880[d]	A	G	0.49	**1.16 (1.00, 1.35)**	$\mathbf{2.73 \times e^{-2}}$	**0.86 (0.20, 1.52)**	$\mathbf{5.30 \times e^{-3}}$
9	120939712	*TRAF1*	rs10760130[e]	G	A	0.46	**1.17 (1.00, 1.36)**	$\mathbf{2.21 \times e^{-2}}$	0.12 (−0.50, 0.74)	$3.51 \times e^{-1}$
9	120942809	*TRAF1/C5-OT1*	rs10818488[e]	A	G	0.46	**1.18 (1.01, 1.37)**	$\mathbf{1.90 \times e^{-2}}$	0.18 (−0.44, 0.81)	$2.84 \times e^{-1}$
9	120944104	*TRAF1/C5-OT1*	rs2900180[f]	T	C	0.38	**1.16 (0.99, 1.35)**	$\mathbf{3.17 \times e^{-2}}$	0.18 (−0.46, 0.82)	$2.93 \times e^{-1}$
9	136370636	*CARD9*	rs59902911[g]	T	C	0.03	**1.66 (1.05, 2.62)**	$\mathbf{1.51 \times e^{-2}}$	**4.65 (2.87, 6.42)**	$\mathbf{1.46 \times e^{-7}}$
10	52309426	*PARP1*	rs1896367	T	C	0.41	**1.15 (0.99, 1.34)**[c]	$\mathbf{3.76 \times e^{-2}}$	0.23 (−0.40, 0.86)	$2.35 \times e^{-1}$
11	112164735	*IL18*	rs1946518	T	G	0.40	0.92 (0.79, 1.08)	$1.54 \times e^{-1}$	**−0.60 (−1.24, 0.04)**[c]	$\mathbf{3.30 \times e^{-2}}$
13	101329420	*NALCN/ITGBL1*	rs506746	T	C	0.15	**0.82 (0.67, 1.02)**[c]	$\mathbf{3.52 \times e^{-2}}$	**−1.11 (−1.99, −0.23)**	$\mathbf{6.65 \times e^{-3}}$
16	27362551	*IL4R*	rs1805011[h]	C	A	0.12	**1.26 (0.99, 1.59)**[c]	$\mathbf{2.82 \times e^{-2}}$	**1.25 (0.25, 2.25)**	$\mathbf{7.10 \times e^{-3}}$
19	54293995	*LILRA3*	rs103294	T	C	0.21	**0.83 (0.69, 1.00)**	$\mathbf{2.71 \times e^{-2}}$	−0.39 (−1.19, 0.41)	$1.70 \times e^{-1}$
Previously replicated non-HLA associations not replicating in NOAR[i]										
1		*FCGR2B*	rs1050501				Not available in the imputed NOAR data set			
1	157701026	*FCRL3*	rs7528684	G	A	0.46	1.10 (0.94, 1.28)	$1.13 \times e^{-1}$	−0.44 (−1.10, 0.22)	$9.48 \times e^{-2}$
1	206773552	*IL10*	rs1800896	T	C	0.49	0.92 (0.79, 1.06)	$1.16 \times e^{-1}$	−0.43 (−1.04, 0.17)	$8.09 \times e^{-2}$
1		*FcγR3A*	rs396991				Not available in the imputed NOAR data set			
1	17336144	*PADI4*	rs2240340	T	C	0.41	0.90 (0.77, 1.05)	$9.36 \times e^{-2}$	0.06 (−0.58, 0.70)	$4.27 \times e^{-1}$
1	113834946	*PTPN22*	rs2476601	A	G	0.12	1.04 (0.83, 1.32)	$3.57 \times e^{-1}$	0.23 (−0.71, 1.16)	$3.19 \times e^{-1}$
2	191099907	*STAT4*	rs7574865	T	G	0.22	1.15 (0.96, 1.38)	$6.47 \times e^{-2}$	0.01 (−0.74, 0.76)	$4.92 \times e^{-1}$
3	9753859	*OGG1*	rs3219008	G	A	0.22	0.96 (0.80, 1.15)	$3.22 \times e^{-1}$	−0.12 (−0.88, 0.64)	$3.81 \times e^{-1}$
7	22727026	*IL6*	rs1800795	C	G	0.44	1.06 (0.91, 1.23)	$2.40 \times e^{-1}$	−0.05 (−0.70, 0.61)	$4.44 \times e^{-1}$
10	52309426	*DKK1*	rs1896367[j]	T	C	0.41	1.15 (0.99, 1.34)	$9.62 \times e^{-1}$	0.23 (−0.40, 0.86)	$2.34 \times e^{-1}$
13	42581032	*RANKL/TNFSF11*	rs2277438	G	A	0.17	1.00 (0.82, 1.22)	$4.97 \times e^{-1}$	−0.13 (−0.96, 0.70)	$3.78 \times e^{-1}$
16	27344882	*IL4R*	rs1805010	G	A	0.45	1.12 (0.97, 1.31)	$6.58 \times e^{-2}$	−0.26 (−0.86, 0.34)	$1.94 \times e^{-1}$
19		*TGFβ1*	rs1982073				Not available in the imputed NOAR data set.			

Chr, chromosome; MAF, minor allele frequency; OR odds ratio.

[a] Results for SNPs from Table 1 reaching a *P* of <.05 for their association with either erosions or Larsen score models in NOAR. We report uncorrected 1-sided *P* values to test for associations in a predefined direction based on previous evidence. Full results are available in Supplementary File S2, Tabs 2 and 3. Chromosome position is given in reference to Build38. A1 refers to the minor allele and A2 refers to the major allele. All reported effect sizes are given with reference to the minor allele. Effect sizes for erosions are given as odds ratios and effect sizes for Larsen score are given as *β* coefficients. All results are reported with 95% CIs.

[i] Results for SNPs from Table 1, which did not replicate in this study but did replicate in at least 2 independent cohorts and reported in at least 2 independent publications. Note that other criteria could be applied to the list of SNPs in Table 1 to extract additional associations likely to represent true positive associations (eg, replication in multiple cohorts within 1 single publication or the presence of additional functional data, like correlation with expression or functional *in vitro* data).

[b] The C allele was previously found to be protective in a previous publication in keeping with NOAR [58]. However, another publication showed an opposite direction of effect [57].

[d] Chromosome 6 SNPs were checked for linkage disequilibrium (LD) with the HLA, via tagging SNP rs660895: (Supplementary Table S4), and none of the above were found to be in LD with the HLA. All were also tested with the shared epitope in the final models, which in most cases did not substantially alter the results. However, rs394581 lost significance, although this was borderline and may be secondary to power.

[e] In LD ($R^2 > 0.7$) with a known susceptibility SNP and with each other ($R^2 = 0.97$), therefore not representing an independent association.

[g] Remained significant after correction for multiple testing in Larsen score model (Benjamin–Hochberg correction, 0.05 false discovery rate).

[h] In the original publication, this SNP has a protective effect in Leiden EAC but was a risk allele in other 3 cohorts (Lund, Groningen and Sheffield, and NARAC). In NOAR, we found the effect direction consistent with risk allele as in other 3 cohorts [115].

[c] 95% CI was around the mean, hence crossed 1 as 1-tailed *P* values were used, to test for associations in a predefined direction based on previous evidence. Boldface values highlight associations which replicated in NOAR with p<0.05.

[f] In LD, $R^2 = 0.72$ with rs10760130, therefore not representing an independent association.

[j] This SNP was associated in NOAR with an effect in the opposite direction of the original publication [99]. Therefore, under the assumption of consistent direction of association across studies, the 1-sided *P* value calculated in this study as follows: 1 − (2-sided *P* value)/2, with the 2-sided *P* values taken from Supplementary File S2, Tab 2.

(rs3812553), located in DNLZ/CARD9, was predicted to be highly likely damaging by PolyPhen2 (score = 0.996) [25]. Whether this results in loss or gain of function, however, is unknown.

The abovementioned statistical and functional evidence strongly implicates a number of candidate SNPs within the *CARD9* genomic region on chromosome 9 influencing radiographic trajectory of patients with RA through modulation of *CARD9* expression in immune cells.

GO pathway analysis

Results of GO pathway analysis of genes in Table 3 are shown in Supplementary File S2, Tab 15. This points almost exclusively towards an involvement of immune cell types and pathways, in particular of the adaptive immune response (including Th1, Th2, and Th17 pathways) and the regulation of cytokine production (including the regulation of nuclear factor κB transcription factor activity). There are also a minority of significant

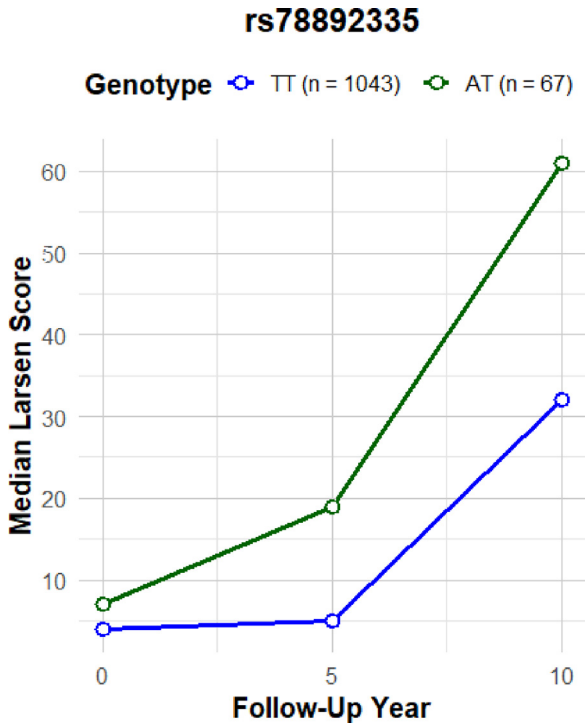

Figure 3. Median Larsen score according to genotype of rs78892335 *ENTR1* over time. Median Larsen score at follow-up years 0, 5, and 10 of patients with different genotypes of SNP rs78892335 *ENTR1* is shown. TT denotes those patients homozygous for the major allele, and AT are heterozygous. Only 1 patient was homozygous (AA) for the minor allele and had only baseline data; therefore, not included in this graph. Patients who had a copy of the minor allele (A) had a more severe radiographic changes compared with those without.

pathways, which suggest musculoskeletal and stromal processes, not directly related to the immune system. This includes regulation of smooth muscle cell apoptotic processes (GO:0034393; $P = .00695$) and smooth muscle proliferation (GO:0048660; $P = .0131$).

DISCUSSION

HLA polymorphisms associated with RA susceptibility are also associated with severity [6]. However, emerging evidence suggests that genetic mechanisms underpinning susceptibility to disease and its progression are different outside the HLA region. Despite a plethora of reports on genetic associations with radiographic outcome in RA, the characterisation of biological mechanisms leading to poor outcome has remained elusive, as most associations fail to replicate in independent cohorts. Our goal was to identify non-HLA loci that warrant prioritisation for future research and clinical application, through (1) review of all reports on radiographic severity in RA across ancestries, (2) independent validation in a large cohort, and (3) gaining biological insights into mechanisms of disease prognosis.

We identified 139 independent genetic associations with radiographic damage in RA reported in the literature between 1998 and 2022. Of those, 15 independent SNPs (Table 3) associated with radiographic progression in NOAR and only 1 of them mapped to a known susceptibility locus (*TRAF1/C5*). This suggests certain genetic factors may not trigger a disease process, but could be implicated in the perpetuation of an inflammatory response, and thus joint damage, after disease onset. In addition, we identified 13 loci (Table 3), which, despite their lack of significant association in this study, had independently replicated before November 2022. Therefore, they represent associations with radiographic damage in RA as likely to be true positive associations as the 15 loci replicated in this study. Several factors could explain a lack of association in our study: (1) different ancestries and MAF between the original cohort and NOAR; (2) differences in demographic and clinical cohort characteristics (including differences in the proportion of seropositive patients and treatment regimens); (3) insufficient power in NOAR (several *P*- values are close to the significance threshold in Table 3); (4) differences in analytical techniques and methodologies. Various methodological factors can impact replication of genetic findings across cohorts. These could be differences in genetic models (e.g., additive vs. recessive), different methods used to measure radiographic damage, varying approaches to assessing progression over time or to adjust for the effect of treatment. This heterogeneity across studies highlights a key challenge in identification of genetic factors associated with prognosis.

One SNP (rs59902911) remained significant in this study after multiple testing. This SNP is located within the *CARD9* (caspase-recruitment domain 9) gene, which has not been associated with susceptibility to RA. This association was previously reported in a cohort of in 424 European American patients with RA [45]. Specifically, the minor allele (T) was associated with increased Sharp score ($\beta = 0.86$; $P = 1.01 \times 10^{-6}$) [45]. In the NOAR cohort, this effect was replicated; the minor allele (T) was also associated with increased Larsen score ($\beta = 4.65$; 95% CI, 2.87-6.42; $P = 1.46 \times 10^{-7}$) and with increased odds of erosions (OR, 1.64; 95% CI, 1.04-2.60; $P = 0.015$). Notably, this effect was independent of anti-CCP status. Further analysis of this genetic locus revealed 30 SNPs in the 95% CSS, in which the minor allele of the lead SNP (rs78892335) reached genome-wide significance ($\beta \pm SE = 4.78 \pm 0.83$; $P = 9.01 \times 10^{-9}$). The minor allele of this intronic SNP located in the nearby *ENTR1* gene increases expression of *CARD9* in B, $CD4^+$ and $CD8^+$ T cells, monocytes and neutrophils. *CARD9* plays an integral role in the immune system through upregulation of inflammatory cytokines such as IL-6, TNF, and interferon γ, and processes such as maturation of antigen-presenting cells, activation of T cells, neutrophil recruitment, and polarisation of macrophages. This gene has been associated with susceptibility to multiple autoimmune diseases including inflammatory bowel disease and ankylosing spondylitis, despite its lack of association with RA susceptibility in a large multiancestry meta-analysis comprising over 276,000 individuals [134,136].

A further example found in this study was rs2243250, located in the *IL-4* gene. Hussein et al, in a small study of 172 patients of which the majority were positive for anti−anti-CCP (91%), found that the minor allele (T) was associated with a 2-fold increased risk of erosions (OR, 2.04; 95% CI, 1.26-3.30; $P = .024$). In NOAR, the minor allele was also associated with increased propensity to erosive change and increased Larsen score. Patients with the TT genotype were found to have lower levels of serum IL-4 compared with those who possessed the CC genotype. IL-4 has a pivotal role in immunoregulation through modulation of macrophage expression profile, reduction of interferon gamma from Th1 cell and polarisation towards a Th2 phenotype [137]. A $IL\text{-}4^{-/-}$ mouse arthritis model demonstrated a greater severity of disease [138,139]. IL-4 is thought to have a dual antiarthritic effect [140], through both inhibition of cartilage degradation and osteoclastogenesis [141−145].

Anti-CCP positivity has been consistently associated with worse prognosis, including higher severity of radiographic damage [3,146]. There is also evidence that anti-CCP positivity is associated with improved response to tocilizumab, abatacept,

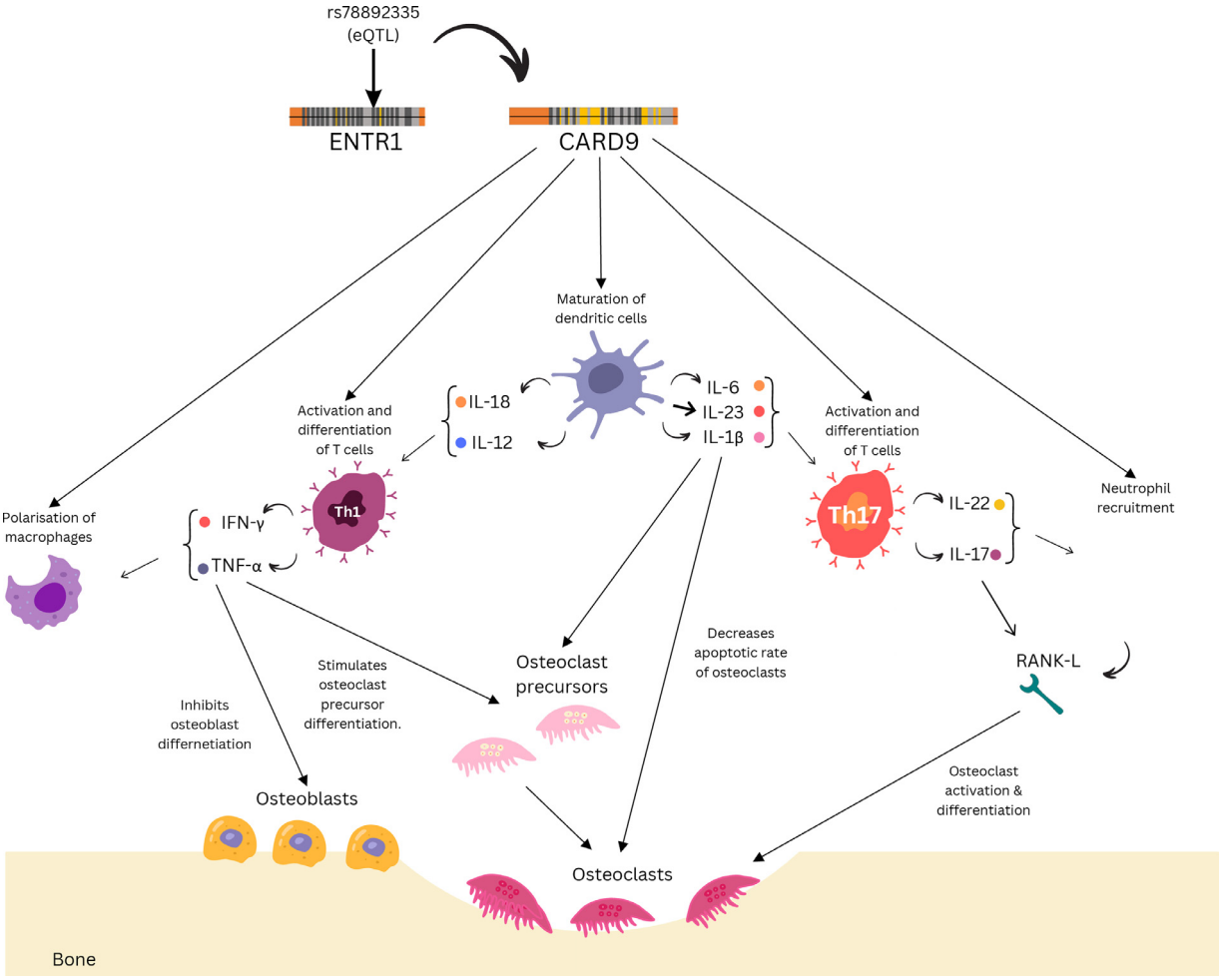

Figure 4. Potential role of rs78892335 (ENTR1) in rheumatoid arthritis (RA). The potential mechanisms by which rs78892335 located on the *ENTR1* gene may lead to increased disease activity and subsequent radiographic damage in RA. rs78892335, an intronic SNP located on the *ENTR1* gene, regulates expression of *CARD9* (minor allele increases expression). CARD9 is involved in both the innate and adaptive immune response through mediation of cytokines as represented in the diagram [134]. Many of these cytokines are known to have potential effects on bone through acting on osteoblasts and osteoclasts. Tumour necrosis factor (TNF) α stimulates osteoclast precursor differentiation through a number of mechanisms including upregulating expression of c-FMS (colony-stimulating factor-1 receptor). It also inhibits osteoblast differentiation though inhibition of RUNX2 and increasing expression of RANKL and M-CSF in osteoblast lineage cells, as well as inducing osteoblast apoptosis. Interleukin (IL)-1 increases osteoclastogenesis and decreases rate of apoptosis. IL-6 stimulates prostaglandin (PG)E_2 synthesis and thereby increases RANKL, thus increasing osteoclastogenesis indirectly. IL-17 increases osteoclastogenesis through induction of RANKL and RANK and upregulates IL-6 through TNFα [135]. This heightened osteoclast activity and inhibition of osteoblast function results in net loss of bone and leads to increase erosive changes in RA.

Table 4
Predicted consequence of exonic SNPs in CARD9 region

Chr	Position	SNP rsID	R^2 with rs78892335	Major allele	Minor allele	MAF	β Coefficient	*P*	Gene	CADD	Synonymous?	Exon	PolyPhen2
9	139256495	rs3812553	0.87	G	T	0.04	4.54	$5.32 \times e^{-7}$	*DNLZ:CARD9*	21.3	No	Exon 3	Probably damaging (score, 0.996)
9	139265870	rs11145769	0.85	G	A	0.04	4.31	$1.2 \times e^{-6}$	*CARD9*	14.84	Yes	Exon 3	
9	139265088	rs59902911	0.90	C	T	0.04	4.65	$2.92 \times e^{-7}$	*CARD9*	14.43	Yes	Exon 5	
9	139270876	rs3812561	0.90	G	A	0.04	4.66	$2.4 \times e^{-7}$	*SNAPC4*	7.417	No	Exon 22	Benign (score, 0.021)
9	139316459	rs11145972	0.87	C	T	0.04	4.62	$2.69 \times e^{-7}$	*PMPCA*	0.824	No	Exon 6	Score not available
9	139301960	rs3812580	0.95	G	A	0.04	4.58	$3.54 \times e^{-7}$	*SDCCAG3*	0.292	Yes	Exon 4	

Within the 95% credible SNP set (CSS) for rs59902911, there were 6 exonic SNPs, shown in this table. These were all in high LD with the lead SNP (SNP with the lowest *P*) *rs78892335* and included the index SNP (original association) *rs59902911*. β Coefficients and *P* values for association with Larsen score in NOAR are displayed. Three of these variants were synonymous, meaning they do not cause a change in amino acid sequence, and 3 were nonsynonymous, leading to changes in the amino acid sequence of the encoded protein. Nonsynonymous variants may potentially impact protein function and thus contribute to the observed phenotypic differences. PolyPhen2 is a tool used to predict potential impact of nonsynonymous changes, and scores are displayed in the table [25]. Of note, rs3812553, located on *DNLZ:CARD9*, was predicted to be highly likely damaging. CADD scores, from FUMA, for each of these SNPs are also displayed (see Methods) [20,22,23].
CADD, combined annotation–dependent deletion; Chr, chromosome; LD, linkage disequilibrium; MAF, minor allele frequency; RDB, RegulomeDB.

and rituximab [147,148]. Establishing whether genetic associations of radiographic severity are related to anti-CCP status is crucial to inform functional mechanisms and whether genetic information is likely to contribute to prediction in clinical practice. For example, rs10760130 (*TRAF1*) appears to influence radiographic severity primarily through association with anti-CCP positivity.

Furthermore, it is increasingly recognised that seropositive RA may have distinct genetic mechanisms compared with seronegative RA. For instance, rs59902911 (*CARD9*) exhibited a greater effect in anti-CCP−positive patients, suggesting a potential interaction with anti-CCP−related pathways. This highlights the heterogeneity of genetic contributions to RA severity and underscores the importance of stratifying analyses by anti-CCP status in future research.

One main strength of the NOAR cohort is the recruitment of patients very early in the disease course, before they satisfy classification criteria for RA. Inception cohorts typically include a larger proportion of anti-citrullinated protein antibodies−negative patients [2,149] and patients with a wider range of radiographic damage than cohorts of patients with established disease from secondary or tertiary care settings. In addition, a large proportion of patients remained untreated in NOAR and a very low proportion were treated with modern strategies, known to diminish radiographic damage. Since we adjusted for the cumulative effect of various treatments, our study design would likely capture the natural evolution of the disease. However, the same setting can also be a limitation, as it favours misclassification − that is, the inclusion of seronegative arthritides other than RA. Historically, data analysis in NOAR, performed both in IP (which will capture seronegative RA better than classification criteria might) [150] and in RA, has led to similar conclusions [2,10]. Similarly, for this study, we performed our analysis in IP, in patients satisfying the ACR 1987 criteria for RA (Supplementary File S2, Tabs 6 and 7) and in patients satisfying the EULAR/ACR 2010 criteria (Supplementary File S2, Tabs 6 and 7) for all SNPs. As an improvement to previous genetic studies in NOAR, we excluded patients with an alternative diagnosis. We also tested the level of correlation of effect sizes between IP and RA and observed a very strong association (β coefficient > 0.8 between effect sizes for Larsen scores in IP and 2010 RA with $P < 7.82 \times 10^{-54}$). This increases our confidence that misclassification is not a major issue in this study.

In summary, we provide a comprehensive list of validated genetic associations with RA outcome and demonstrate that non-*HLA* severity polymorphisms, despite lack of association with disease susceptibility, can reach genome-wide significance and point towards genetic mechanisms of radiographic outcome. Our findings support the need for dedicated genetic studies looking specifically at genetic drivers of disease severity and outcomes. There is evidence for this across other autoimmune diseases such as inflammatory bowel disease and multiple sclerosis [13,151]. Further research could include severity specific GWAS and development of polygenic risk scores, which would require prospective testing in an inception cohort to determine whether these approaches have clinical utility and are cost-effective.

Competing interests

All authors declare they have no competing interests.

CRediT authorship contribution statement

Seema Devi Sharma: Writing − review & editing, Writing − original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Lysette Marshall:** Methodology, Investigation, Formal analysis. **Alice Storrie:** Writing − original draft, Formal analysis. **John Bowes:** Writing − original draft, Visualization, Methodology, Conceptualization. **Alexander MacGregor:** Writing − review & editing, Funding acquisition, Data curation, Conceptualization. **Max Yates:** Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Andrew P Morris:** Writing − review & editing, Writing − original draft, Methodology, Formal analysis. **Suzanne Verstappen:** Writing − review & editing, Methodology, Data curation. **Anne Barton:** Writing − review & editing, Writing − original draft, Visualization, Supervision, Investigation, Conceptualization. **Hanna van Steenbergen:** Methodology, Investigation. **Rachel Knevel:** Supervision, Methodology, Investigation. **Sebastien Viatte:** Writing − review & editing, Writing − original draft, Visualization, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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Patient consent for publication

The Norfolk Arthritis Register (NOAR) is an inception cohort of patients with inflammatory polyarthritis recruited since 1989 and followed prospectively for up to 20 years. All patients were recruited after informed consent.

Ethics approval

Ethical approval was granted by the Norwich Research Committee (NOAR − REC Ref 2003/075, December 18, 2003, Norwich Local Research Committee [NHS]).

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ard.2025.04.007.

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