FCRL3 –169C/C Genotype Is Associated with Anti-citrullinated Protein Antibody-positive Rheumatoid Arthritis and with Radiographic Progression

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ABSTRACT. ***Objective.*** Studies of Caucasian populations have shown conflicting results concerning the association between a promoter polymorphism –169T>C of the Fc receptor-like 3 (*FCRL3*) gene and rheumatoid arthritis (RA). It is unknown whether *FCRL3* is associated with autoantibody status and disease severity. We investigated associations between *FCRL3* –169T>C and autoantibody status and joint damage in patients with RA.

Methods. A total of 652 Norwegian patients with RA from 2 cohorts and 981 Norwegian controls, previously genotyped for *FCRL3* –169T>C (rs7528684), were studied. Data on anticitrullinated protein antibodies (ACPA) and rheumatoid factor (RF) were available. The EURIDISS cohort (disease duration ≤ 4 yrs at baseline) was followed longitudinally, with assessment of radiographic hand damage at baseline and after 10 years (n = 117) according to the van der Heijde-modified Sharp score.

Results. We found significant associations with ACPA-positive RA for both the C allele (OR 1.28, 95% CI 1.08–1.52, p = 0.004) and the C/C genotype (OR 1.57, 95% CI 1.18–2.10, p = 0.002). Similar associations were seen with RF-positive RA. No association was found with ACPA-negative or RF-negative RA. The C/C genotype was found to be associated with 10-year radiographic progression in multivariate linear and logistic regression analyses, after adjustment for ACPA, erythrocyte sedimentation rate, age, and sex.

Conclusion. The promoter polymorphism of *FCRL3* was associated with autoantibody-positive RA. Despite the low number of patients, the C/C genotype of the *FCRL3* polymorphism consistently and independently predicted radiographic progression. These findings suggest that *FCRL3* is involved in both disease susceptibility and progression. (First Release Sept 1 2011; J Rheumatol 2011;38: 2329–35; doi:10.3899/jrheum.110489)

Key Indexing Terms:
RHEUMATOID ARTHRITIS ANTICITRULLINATED PROTEIN ANTIBODIES
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Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disorder mainly affecting the joints. The etiology is still largely unknown, but it is likely caused by an intricate interplay of genetic and environmental risk factors. The disease course of RA is heterogeneous and genetic factors are believed to influence not only disease susceptibility but also severity, such as joint destruction[1]. The main genetic determinant for RA susceptibility is defined as certain alleles at the HLA-DRB1 gene; however, genome-wide association studies (GWAS) have led to the discovery of more than 30 RA susceptibility loci, many of which seem to be involved in multiple autoimmune diseases[2]. One such gene is the Fc receptor-like 3 gene, *FCRL3* 169T>C (rs7528684), where a functional polymorphism in the promoter region was first found to be associated with RA in a Japanese population[3]. Replication studies of this gene have shown inconsistent results[3,4,5,6,7,8,9,10,11,12], and metaanalyses suggest the gene may be associated with RA in the Asian population but not in the white population[13,14]. However, a recent GWAS of autoantibody-positive RA patients of European descent found evidence of an association with the *FCRL3* gene (rs3761959; $r^2 = 1$ with rs7528684, $P_{GWAS} = 0.001$, OR 1.08)[15]. Further, in the initial study by Kochi, *et al*, a correlation between the number of susceptibility alleles and anti-citrullinated protein antibodies (ACPA) was found[3].

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Taking these findings into account, it might seem that this gene may also contribute risk in a European population, but the risk appears to be of moderate magnitude and might be confined only to autoantibody-positive RA.

The precise function of FCRL3 is still unknown. It has a structural homology similar to the classical Fc receptors, and it is known to be present on both T and B cells. In several replication studies, the C/C genotype of the *FCRL3* –169T>C polymorphism has shown the strongest association to RA[3,4,5,12]. Further, the C allele of the *FCRL3* polymorphism has been shown to alter the binding affinity of nuclear factor-κB (NF-κB) and cause increased transcription of *FCRL3*, and healthy individuals who were homozygous (C/C) for the risk allele had higher expression levels of the FCRL3 protein on their B cells[3,16]. It has been hypothesized that increased expression of FCRL3 may cause B cell abnormalities, and may therefore play a role in the production of ACPA or rheumatoid factor (RF)[3].

It is unclear whether the *FCRL3* –169T>C polymorphism plays a part in the development of disease severity. However, there are several examples of polymorphisms that initially were shown to increase susceptibility to RA, and later were found also to influence disease severity[17,18,19]. In order to elucidate whether there is an association with severity it is essential to have longitudinal followup data and a robust endpoint.

The 2 aims of our study were (1) to replicate the proposed association of *FCRL3* –169 C/C genotype with ACPA-positive RA; and (2) to explore whether the *FCRL3* –169 C/C genotype had an effect on rate of joint destruction in a cohort of patients followed longitudinally before biological drugs were established therapy.

MATERIALS AND METHODS

Patients and radiographic followup. In our study we included a total of 652 Norwegian patients with RA, all fulfilling the American College of Rheumatology criteria for RA[20], and 981 healthy controls. All individuals had previously been genotyped for the *FCRL3* rs7528684 polymorphism in a study focusing on genetic susceptibility[4]. We had acquired new additional data on antibody status for most patients, and all patients (N = 652) had either ACPA status (N = 628) and/or RF status (N = 629) available for the current study. The patients were from 2 RA cohorts: the Oslo RA Register (ORAR) and the Norwegian arm of the European Research on Incapacitating Diseases and Social Support (EURIDISS) (Figure 1). Followup data of both cohorts have been described[18,21,22].

The Regional Committees for Research Ethics in Eastern and Southern Norway and the data inspectorate approved our study. Patients gave written informed consent before participation.

Patients from the EURIDISS cohort (n = 205) had < 4 years' disease duration at baseline (mean 2.3 yrs) in 1992 and were followed longitudinally with extensive data collection, including radiographs of hands at baseline, 1, 2, 5, and 10 years. Radiographs were scored according to the van der Heijde-modified Sharp score (SHS) as described[23,24]. This cohort was established before biological disease-modifying antirheumatic drugs (DMARD) became available, and patients were treated according to clinical judgment by their rheumatologist during the study. At baseline and at 10-year followup, 52% (10-yr followup 46%) were receiving synthetic DMARD and 27% (10-yr followup 36%) used prednisolone. At the 10-year followup 12% of patients were using anti-tumor necrosis factor (anti-TNF) drugs, while none had been at baseline. Only patients from the EURIDISS study who had had radiographs both at baseline and at 10 years (N = 117) were included in the severity analyses (Figure 1). The 447 ORAR patients had a mean age at disease onset of 47.3 years and mean disease duration of 12.9 years at inclusion. Patient demographics and baseline characteristics, for the total material and for the subgroup of patients with 10-year radiographic followup, are given in Table 1.

Laboratory analyses. Serum samples from patients from the ORAR cohort were collected in 1996-97 and had been stored at –70°C. IgG antibodies against second-generation cyclic citrullinated proteins (CCP2) were analyzed in 607 patients using a second-generation Diastat™ ELISA, and > 5 U/ml was considered positive, according to the manufacturer's instructions (Axis Shield Diagnostics Ltd., Dundee, UK). Sera samples from ORAR were not reexamined for RF, but results of routine tests at inclusion were available and a titer ≥ 64 on the Waalers test was considered RF-positive as described[21]. In the EURIDISS cohort, serum was taken at baseline, 5, and 10 years and analyses of IgM RF antibodies and IgG antibodies against ACPA (CCP2) were undertaken as described[22]. Patients' samples were considered positive if they had at least 1 measurement above cutoff.

Statistical analyses. Analyses were carried out using SPSS 17 (SPSS, Chicago, IL, USA). The chi-square test was used to test for associations between proportions such as the genotype and disease state, and the Wolf-Haldane method was used when calculating OR and 95% CI. Group data are presented as means (SD) or medians [interquartile range (IQR)]. Group comparisons were performed by Student's t test or Mann-Whitney U test according to the distribution of the data.

Cumulative probability plots are presented to compare 10-year radiographic progression (i.e., 10-year change in SHS) in patients carrying the risk genotype (C/C) with patients carrying C/T or T/T genotypes. In a second cumulative probability plot, patients were not only stratified according to genotype (C/C vs C/T or T/T) but also for ACPA status. We performed multivariate linear regression analysis to test whether the risk genotype was associated with 10-year SHS. In the linear regression analysis the outcome variable, 10-year SHS, was log-transformed due to a skewed distribution, and we adjusted for factors known to be associated with radiographic progression such as ACPA status, inflammation measured by ESR (calculated as mean ESR measured at baseline, 1 year, and 2 years), age, and sex. Relevant interactions were tested, and colinearity between the covariates was assessed. Data were available for all patients at all timepoints. DMARD use at baseline (yes/no) was also included in the linear model to test whether there was confounding by indication. To evaluate the robustness of our model, we explored whether the risk genotype could predict radiographic progression in a logistic regression model. In this analysis the outcome variable was dichotomized into 2 groups, nonprogressors (≤ 10 units change in SHS over 10 years) and progressors (> 10 units change over 10 years), as previously used in this cohort[18]. The logistic regression was adjusted for the same covariates as in the linear model.

RESULTS

Associations with antibody status. The genotype data suggest a recessive mode of inheritance, as there was a higher frequency of patients having C/C (and not the C/T or T/T) genotype compared with controls (Table 2). We found a significant association of the C allele and C/C genotype of the *FCRL3* –169T>C single-nucleotide polymorphism (SNP) with both ACPA-positive and RF-positive RA compared with controls (Table 3). In contrast, no association was observed among the antibody-negative patients. The autoantibody-positive patients showed significantly higher frequencies of both the C allele and the CC genotype compared with autoantibody-negative patients (Table 3).

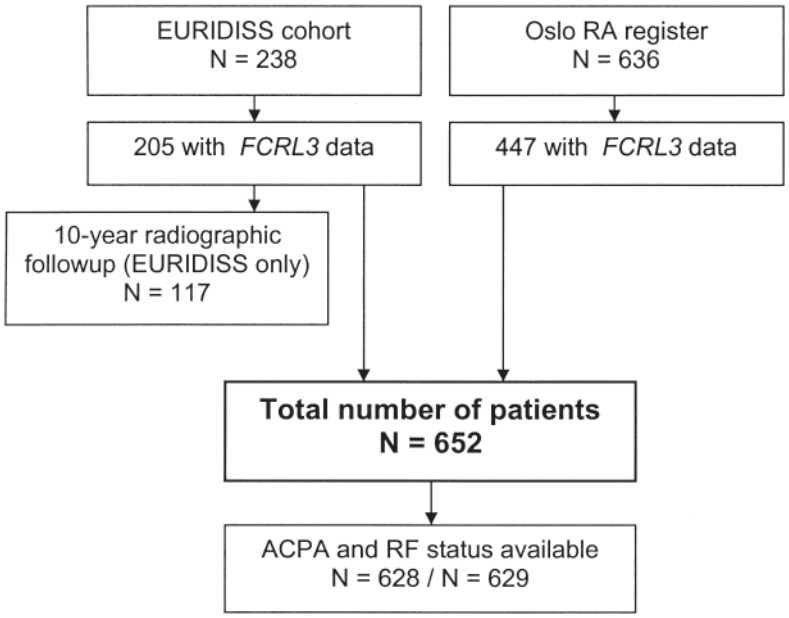

Figure 1. Patient groups and data available for the study.

Table 1. Patient demographics, serological status, and shared epitope in all patients, as well as baseline disease-related characteristics in the subgroup of patients with 10-year followup. Values are N (%) for continuous variables or mean with standard deviation (SD) or median with interquartile range (IQR; 25,75). HAQ, SHS, CRP, ESR, and DMARD use are baseline values.

Characteristic	Total, N = 652	EURIDISS Patients with Radiographs, N = 117
Female	498 (76.4)	90 (76.9)
Age at disease onset, yrs	48.1 (15.6)	48.7 (12.8)
ACPA-positive	384 (60.0)	73 (62.4)
RF-positive	330 (52.6)	69 (59.0)
Shared epitope-positive	473 (72.5)	91 (78.4)
HAQ score	—	0.90 (0.61)
SHS score	—	7.2 (13.0)/2 [0–7.5]
CRP, mg/l	—	4.85 [1.8–11.7]
ESR, mm/h	—	21.0 [11.5–38.0]
DMARD use	—	62 (53.0)

ACPA: anti-citrullinated protein antibodies; RF: rheumatoid factor; HAQ: Health Assessment Questionnaire; SHS score: van der Heijde modified Sharp score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DMARD: disease-modifying antirheumatic drugs; EURIDISS: European Research on Incapacitating Diseases and Social Support.

Radiographic progression. The median baseline SHS score was higher in patients carrying the C/C genotype [5 (IQR 0, 18)], compared to patients with the C/T or T/T genotype [0 (IQR 0, 7)]. The 10-year change in SHS score for both groups (C/C and C/T or T/T) is displayed in a cumulative probability plot (Figure 2A). There was a significant difference on the group level, with median values for the 10-year SHS as follows: C/C = 39.5 (IQR 14.3, 65.5) vs C/T or T/T = 13 (IQR 2, 42; p = 0.01). The significant difference in radiographic progression between the 2 groups (C/C vs C/T or T/T) was also present in the subset of ACPA-positive patients, with median 10-year SHS scores as follows: C/C = 50 (IQR 22, 70.5) vs C/T or T/T = 31.5 (IQR 9.3, 55.3; p = 0.04; Figure 2B). ACPA-negative patients had a median 10-year SHS = 4 (IQR 0, 14.5); however, there were too few patients to stratify ACPA-negative patients according to genotype (ACPA-negative patients, C/C: N = 5; C/T or T/T: N = 39).

We examined whether the C/C genotype of the *FCRL3* –169T>C SNP could predict radiographic progression by using a linear regression model. Both the univariate and multivariate models demonstrated a significant effect of the C/C genotype on 10-year change in SHS score (Table 4). The fraction of the variability in radiographic progression (R^2) explained by the C/C genotype was 5.2% in the univariate analysis, and 3.0% in the multivariate analysis, indicating a small but significant effect of the *FCRL3* polymorphism on joint damage. Treatment with DMARD at baseline (yes/no) was also included as an additional covariate and did not alter the result, i.e., the C/C genotype was still a significant predictor of radiographic progression (p = 0.01).

To test the robustness of our model, we also performed logistic regression, comparing progressors (> 10 SHS units per 10 years) with nonprogressors (≤ 10 SHS units per 10 years) with the same adjustment as in the linear analysis. The results were consistent, i.e., the patients carrying the C/C genotype were more likely to be radiographic progressors over the 10-year followup period (OR 4.95, 95% CI 1.24–19.7, p = 0.02).

Table 2. *FCRL3* genotype counts and frequencies.

	TT (frequency)	CT (frequency)	CC (frequency)
Controls	316 (32.2)	503 (51.3)	162 (16.5)
ACPA-negative	80 (32.8)	125 (51.2)	39 (16.0)
ACPA-positive	104 (27.1)	189 (49.2)	91 (23.7)
RF-negative	105 (35.1)	146 (48.8)	48 (16.1)
RF-positive	84 (25.5)	170 (51.5)	76 (23.0)

ACPA: anti-citrullinated protein antibodies; RF: rheumatoid factor.

Table 3. Association tests for the C allele and C/C genotype at *FCRL3* with autoantibody-positive and negative RA.

	Frequency C Allele	Allele Test C vs T OR (95% CI)	p	Frequency C/C Genotype	Genotype Test C/C vs C/T or T/T OR (95% CI)	p
Controls	0.42			0.17		
ACPA-positive	0.48	1.28 (1.08–1.52)	0.004	0.24	1.57 (1.18–2.10)	0.002
ACPA-negative	0.42	0.98 (0.80–1.20)	0.83	0.16	0.97 (0.66–1.41)	0.87
RF-positive	0.49	1.30 (1.10–1.56)	0.003	0.23	1.52 (1.12–2.06)	0.008
RF-negative	0.40	0.93 (0.77–1.12)	0.47	0.16	0.97 (0.69–1.38)	0.88
ACPA positive vs negative		1.33 (1.06–1.67)	0.02		1.56 (1.05–2.32)	0.02
RF positive vs negative		1.40 (1.12–1.75)	0.003		1.62 (1.07–2.45)	0.02

ACPA: anti-citrullinated protein antibodies; RF: rheumatoid factor.

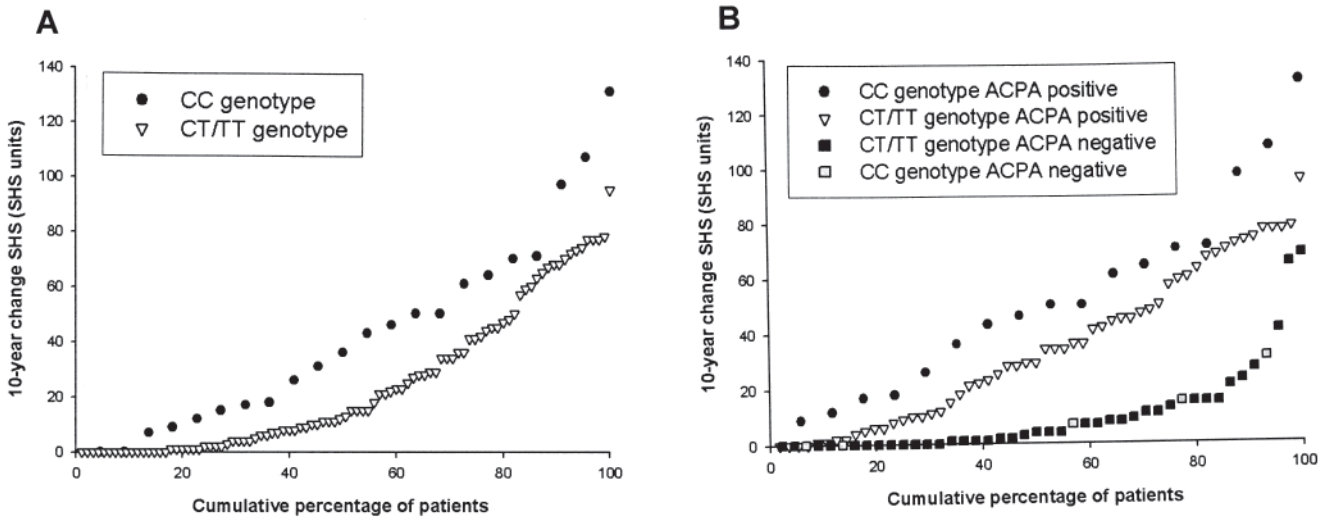

Figure 2. A. Cumulative probability plot of progression of 10-year van der Heijde-modified Sharp score (SHS) in patients with C/C genotype (N = 22) and C/T or T/T genotype (N = 95). B. Cumulative probability plot of 10-year SHS progression in ACPA-positive patients with C/C genotype (N = 17), or C/T or T/T genotype (N = 56). ACPA-negative patients plotted for comparison (N = 44). APCA-negative patients carrying C/C genotype (N = 5) are indicated as gray squares.

DISCUSSION

In this study we confirmed that the C allele and C/C genotype of the *FCRL3* polymorphism was associated with autoantibody status. We also found that the C/C genotype was associated with increased radiographic progression in RA over time. This association was maintained in multivariate analyses after adjusting for ACPA and other disease factors known to predict radiographic progression.

Multiple studies with conflicting results have made it difficult to agree upon whether *FCRL3* is a risk gene for RA. It has been proposed through metaanalyses that the promoter SNP (rs7528684) is a risk variant in the Asian population but not in white Europeans[5,13,14]. Even though these metaanalyses were well powered, a serious limitation is that they did not consider autoantibody status. In the original study by Kochi, *et al*[3] a correlation between number of susceptibility

Table 4. The *FCRL3* C/C genotype as a predictor of 10-year radiographic progression based on univariate and multivariate linear regression analyses.

	Independent Variable	Beta	95% CI	Standardized Beta	p
Univariate	C/C genotype	0.876	0.18–1.57	0.228	0.01
Multivariate	C/C genotype	0.674	0.11–1.23	0.175	0.02
	ACPA	1.32	0.85–1.78	0.424	< 0.0001
	ESR	0.031	0.02–0.05	0.303	< 0.0001
	Age	–0.007	–0.02–0.01	–0.056	0.46
	Sex (female)	0.559	0.08–1.12	0.168	0.02

Dependent variable: Ln 10-year change SHS score. Adjusted R^2 for the multivariate model was 0.38. ACPA: anticitrullinated protein antibodies; ESR: erythrocyte sedimentation rate.

alleles of the *FCRL3* polymorphism and ACPA status was seen. In addition, a recent GWAS that included only autoantibody-positive RA patients of European descent found a modest association between an SNP (rs3761959) in the *FCRL3* gene and RA (OR 1.08, p = 0.001)[15]. This polymorphism has been shown to be in high linkage disequilibrium (r^2 = 1.0) with rs7528684 (*FCRL3* –169T>C)[11], the SNP investigated in our study. Our findings support the initial observation by Kochi, *et al* that *FCRL3* is associated with ACPA- and RF-positive RA. Thus, *FCRL3* appears to confer risk for RA in the Caucasian population; however, the risk might be of small magnitude and confined to autoantibody-positive disease.

There is mounting evidence that genetic risk factors predispose to either ACPA-positive or negative RA[25]. Hence, stratifying patients according to autoantibody status is important when testing for genetic associations. Nevertheless, stratification also reduces the number of patients available for comparison, thus increasing the chance of a type 2 error. In the case of *FCRL3*, the different replication studies that considered autoantibody status have shown conflicting results[3,4,6,7,8,9,10,12,26]. Studies that failed to observe an association may have lacked power due to small sample sizes[6,8,10,11]. Further, the *FCRL3* –169T>C SNP may not be the causal variant, and differential linkage disequilibrium patterns between the promoter polymorphism and the causal variant in different populations may explain the different association results for this marker. In addition, the possibility of multiple risk variants cannot be ruled out.

FCRL3 –169T>C has been associated with several autoimmune diseases including systemic lupus erythematosus, multiple sclerosis, and autoimmune thyroid disease. FCRL3 is present on a variety of immune cells including B cells, T cells, and natural killer cells; however, its function is unknown[16,27]. The proposed risk genotype (C/C) of the promoter polymorphism has been shown to increase expression of the *FCRL3* gene and also to increase the expression of Fc receptor-like 3 on the B cell surface[16]. FCRL3 is especially expressed on germinal-center B cells, and it has been suggested that a gain of function of this gene may affect B cell activity and differentiation[28,29], which highlights a potential role in the formation of autoantibodies in RA. A final clarification of the possible association between *FCRL3* –169T>C and autoantibody-positive RA requires large metaanalyses in which patients are stratified according to autoantibody status.

Our second focus was association with joint damage, and we found that the *FCRL3* –169C/C genotype was associated with radiographic progression over 10 years. Presence of ACPA and a high inflammatory load are both well known predictors of radiographic progression[22,30]. In our study the *FCRL3* –169C/C genotype was an independent predictor of radiographic progression even after adjustment for ACPA and ESR, suggesting that the *FCRL3* gene is related to joint destruction through a mechanism that cannot be explained solely by its association with ACPA. Studies investigating whether there is an association between the *FCRL3* polymorphism and joint destruction have shown conflicting results. In a large Korean study a marginal association between the *FCRL3* gene and erosive disease was found[6]. In another study from Taiwan, the non-risk allele was more common in patients classified as having nondestructive RA[31]. However, both these studies were cross-sectional, making it difficult to interpret causality. One of the strengths of our study was its longitudinal design, with a robust and well-described endpoint. The cross-sectional baseline data also indicated an association between radiographic damage and the *FCRL3* gene, and the cumulative probability plots indicate a difference on an individual level between patients with and those without the risk genotype. As well, the *FCRL3* gene was also a predictor in the longitudinal analyses, with the endpoint both as a continuous and as a categorical variable. The longitudinal data from the EURIDISS cohort have also previously been applied to identify predictors of radiographic progression including shared epitope status, *PTPN22*, ACPA, and anti-MCV level as well as CTX1[18,22,32,33]. This cohort was established in 1992 and the 10-year followup was completed before the era of biological therapy. Nonetheless, 12% of patients were taking anti-TNF medication at the 10-year followup, but they would only have been exposed to this therapy for rather short periods.

Ideally our findings should have been replicated in a similar cohort; however, such cohorts are scarce. A Dutch longitudinal cohort did not find any association[5], but differences in study design and patient characteristics may partly explain the discrepancies in the results. The patients in the Dutch cohort had shorter disease duration at baseline and received more aggressive treatment compared with patients in our study. Importantly, those patients were followed for 4 years, which may be insufficient to detect the small/modest effect on SHS score that we found after 10 years of followup.

One limitation of our study is that only 117 patients from the EURIDISS cohort (N = 238) had 10-year radiographs and DNA and sera samples available for RF and ACPA analyses. One of the challenges with longitudinal observational studies is the problem of missing data that may skew the results. However, baseline characteristics, including baseline SHS scores, number of patients receiving DMARD, ESR, age, and sex, were similar for patients included in the severity analysis to those who were omitted due to missing data (data not shown).

Another limitation is lack of detailed data on treatment during the study period. DMARD treatment could be a possible confounder, either through "confounding by indication" (i.e., patients with known poor prognostic markers will receive more aggressive treatment, thereby reducing the difference in radiographic progression between the risk and non-risk groups), or if by chance patients with the non-risk genotype received more aggressive therapy compared to patients carrying the risk genotype, making the difference in joint progression between the 2 groups appear larger. However, our results did not change when we adjusted for DMARD treatment at baseline (yes/no), or when we adjusted for biological DMARD at 10-year followup (ever/never) (data not shown).

Taken together, our results suggest that the *FCRL3* promoter polymorphism is associated with both ACPA status and radiographic progression in RA. Future well-powered studies are needed to establish these associations. As with other genetic markers such as *PTPN22* and shared epitope status, the role of the *FCRL3* genotype as a clinical predictor of joint damage is limited, as it accounts for only 3% of the variance in radiographic progression (*PTPN22* accounts for 5%, shared epitope for 7%)[18]. Still, increased knowledge concerning genetic factors and pathophysiological pathways that influence joint damage may lead to insight into why the severity of RA varies between individuals.

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