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Original article

The role of rheumatoid arthritis genetic susceptibility markers in the prediction of erosive disease in patients with early inflammatory polyarthritis: results from the Norfolk Arthritis Register

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Abstract

Objectives. Recent whole-genome and candidate gene association studies in RA have identified a number of single nucleotide polymorphisms (SNPs) that predispose to disease with moderate risk. It remains poorly understood how recently identified genetic factors may contribute to RA severity. We therefore sought to investigate the role of recently identified RA susceptibility SNP markers in predicting erosive outcome in patients with recent-onset inflammatory polyarthritis (IP).

Methods. DNA and X-ray data were available for 1049 patients who were registered between 1990 and 2003 with the Norfolk Arthritis Register (NOAR); a primary care-based inception cohort of patients with recent-onset IP. Demographic and clinical data were recorded at inclusion, and at yearly assessments thereafter. Patients were genotyped for 18 SNP markers. The presence of serum anti citrullinated peptide antibodies (ACPAs) was assessed in samples collected at inclusion to the NOAR. The association of serological and genetic markers with poor radiological (Larsen) score at Years 1 and 5, and erosions at Years 1 and 5 was investigated.

Results. Baseline ACPA positivity was associated with erosive disease and higher radiological damage. SNP markers within the *TRAF1/C5* locus were associated with erosive disease at Year 1 [rs2900180: odds ratio (OR) 1.53 (95% CI 1.14, 2.05)] and Year 5 [rs2900180: OR 1.47 (95% CI 1.07, 2.02)]. None of the SNP markers tested was associated with Larsen score.

Conclusion. Our results are in keeping with a previous report and suggest that the *TRAF1/C5* region is associated with risk of development of radiological erosions in IP/RA patients. The finding requires replication in other large data sets.

Key words: Genetic association, Erosions, Inflammatory polyarthritis, Rheumatoid arthritis.

BASIC SCIENCE

Introduction

Increasingly, physicians would like to identify which patients presenting with inflammatory joint disease are likely to develop severe disease before they satisfy ACR classification criteria for RA, so that appropriate treatment can be introduced before irreversible damage occurs. The importance of antibodies directed against citrullinated peptide antibodies (ACPAs) in this regard has been increasingly appreciated in recent years [1–5]. For example, we have reported previously that, in the Norfolk

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Arthritis Register (NOAR), an inception cohort of patients with inflammatory polyarthritis (IP), only 45% of whom satisfied ACR classification criteria for RA at baseline, the presence of ACPA was strongly associated with the development of erosions by 5 years [1]. However, ACPA do not perfectly correlate with severe outcome. For example, in the same study, there were a significant minority of patients who did not have these antibodies at baseline but developed severe disease, as assessed by radiological erosions [1]. Hence, the identification of markers that would refine the accuracy of ACPA in predicting disease severity would be an important clinical advance.

Genetic factors play an important role in determining development of persistent and destructive IP, and are estimated to account for 50–60% of disease susceptibility. In patients of European ancestry, the strongest genetic susceptibility effects are conferred by the *HLA-DRB1* locus on chromosome 6 [6] [the shared epitope (SE)] and the protein tyrosine phosphatase 22 (*PTPN22*) gene on chromosome 1p13 [7]. In terms of disease outcome, the *HLA-DRB1* locus is associated with the development of radiological erosions [8]. The functional susceptibility single nucleotide polymorphism (SNP) within *PTPN22* does not appear to associate with disease outcome in persistent IP or RA [9].

Recent whole-genome and candidate gene disease association studies have identified further non-HLA RA susceptibility loci (i.e. 6q23, *TRAF1/C5, STAT4, IL2RB, KIF5A, PRKCQ, IL2_IL21, CD226, CCL21, CD40, CTLA4, IL2RA, AFF3* and *IL7R*), defined by SNP markers that associate with susceptibility with low-to-moderate risk [10–19]. What is less clearly understood, however, is the role of these SNP susceptibility markers in determining disease outcome as measured by the presence of radiographic erosions in patients with persistent IP.

Using a large primary care-based inception cohort of patients with recent-onset IP, we examined the relationship of baseline prognostic factors, including ACPA positivity, carriage of *HLA-SE* risk alleles and the newly confirmed RA SNP susceptibility markers, with radiological erosion at 1 and 5 years of follow-up.

Methods

Subjects

The NOAR is a primary care-based inception cohort of patients with recent-onset IP. Further details of this register are described elsewhere [20]. In brief, patients aged $\geqslant$16 years at symptom onset, who had synovitis of two or more joints, lasting $\geqslant$4 weeks, and whose symptom onset was after 1 January 1990, are recruited from general practitioners and rheumatologists in the catchment area, formerly covered by the Norwich Health Authority (UK). Ethical approval was obtained from the Norwich District Health Authority Research Ethics Committee, and all participants gave informed consent. Clinical and demographic data were collected by a research nurse via a structured interview and clinical examination shortly after registration (baseline). In addition, DNA and serum samples were collected to permit genetic and serological studies. Excluded from the study were patients who received a clinical diagnosis other than RA, IP, PsA or post-viral arthritis at baseline assessment or subsequent follow-up.

Data collection

Demographic data included age, date of symptom onset and gender. Clinical data included information on DMARD and steroid therapy. X-rays of the hands and feet were taken at 1 and/or 2 years in patients who satisfied ACR criteria for RA (or would satisfy ACR criteria for RA should evidence of erosions be detected), and at 5 years unselectively. They were read independently by two observers using the Larsen method [21] with a third observer arbitrating in case of disagreement. ACPAs were measured using the CCP2 detection kit (positivity $\geqslant$5 U/ml; Axis-Shield, Cambridgeshire, UK) using baseline serum samples. The presence of *HLA-SE* copy number (0, 1 or 2 copies) was detected using a semi-automated reverse hybridization method (Dynal Biotech, Wirral, UK).

Genotyping

Eighteen SNPs were selected for genotyping using Sequenom MassArray technology according to the manufacturer's instructions, using iPLEX chemistry (Sequenom, Hamburg, Germany). The SNPs were markers associated with RA susceptibility in cohorts tested by our group and others and consisted of: rs1160542 (*AFF3*), rs2812378 (*CCL21*), rs763361 (*CD226*), rs4810485 (*CD40*), rs3087243 and rs231775 (*CTLA4*), rs6822844 (*IL2/IL21*), rs2104286 (*IL2RA*), rs743777 (*IL2RB*), rs6897932 (*IL7R*), rs1678542 (*KIF5A*), rs4750316 (*PRKCQ*), rs7574865 (*STAT4*), rs13207033, rs5029937 and rs6920220 (6q23), rs10760130 and rs2900180 (*TRAF1/C5*). Only those SNPs with a genotype success rate of >90% were included in the analysis.

Statistical analysis

Univariate analysis. The IP patients with X-ray data at 5 years (5-year IP cohort) were unselected and are most representative of those in whom the identification of risk factors to inform decisions regarding treatment would be most helpful. First, therefore, logistic regression was used to investigate the association of potential prognostic markers with erosive disease, as a binary outcome, by the 5-year follow-up. Patients were defined as having erosive disease if they had a Larsen score $\geqslant$2 in at least one joint of the hands or feet. Secondly, in order to determine whether markers were associated with the severity or extent of erosive disease in those with erosions, negative binomial regression models were used to investigate the association between potential prognostic markers and Larsen scores by Year 5 in patients with confirmed erosive disease. Negative binomial regression models were employed to model count data, in preference to Poisson regression, to account for any over-dispersion of variance. The subgroup of patients who satisfied the ACR criteria

for RA by the fifth anniversary follow-up (5-year RA subgroup) was analysed separately [22].

The subgroup of patients with X-ray data at 1 year (1-year IP cohort) are not an unselected group. X-rays were only undertaken at Year 1 if the subjects had met or could meet ACR classification criteria for RA. Hence, they represent a more severe subset of all patients presenting with IP and it was hypothesized that markers with evidence of association with erosions in the IP group as a whole may show stronger evidence for association in this more severe subgroup. Therefore, the same analysis was undertaken investigating markers for association with erosions and Larsen score by Year 1 in the 1-year IP cohort as detailed above for the 5-year IP cohort. All the analyses were repeated after adjustment for treatment (i.e. ever treated with DMARDs/steroids following symptom onset) to determine whether this materially altered the findings.

Multivariate analysis. ACPA positivity is strongly predictive of radiographic erosions in RA [1–5]; therefore, SNP markers were investigated in the context of ACPA status. Multivariate logistic regression models were used to investigate the role of SNP markers in predicting erosions at Years 5 and 1 following adjustment for ACPA status, and to investigate SNP markers in the stratum of patients who were either positive or negative for these antibodies. In addition, SNP markers were investigated in the context of *HLA-SE* allele carriage (i.e. carriage of at least one SE allele). All statistical analyses were conducted using Stata version 9 (2005. Stata Statistical Software: Release 9; Stata Corp., College Station, TX, USA).

Results

Study population characteristics

Genotyping data were available from 2611 IP patients, of which 2538 passed genotyping quality control (97% success). Radiological data were available for 1378 patients. One thousand and forty-nine patients had both genotype and X-ray data and remained available to study. Six hundred and sixty-three IP patients had X-ray data available for Year 5 (5-year IP cohort) of whom 489 patients satisfied ACR criteria for RA (5-year RA subgroup), while 761 IP patients had X-ray data available for Year 1 (1-year IP cohort). Three hundred and seventy-five patients were X-rayed at both time points—of 234 patients who were initially non-erosive (by Year 1), 80 (34%) developed erosive disease by Year 5 (all 375 patients satisfied ACR criteria for RA by 5-year follow-up and were included in the 5-year analysis). The characteristics of these patients are summarized in Table 1.

Radiological erosions by Year 5

We have previously reported that the presence of ACPA is associated with the development of erosions [1]. In this extended data set, we again found that ACPA positivity was strongly associated with erosive disease in the 5-year IP cohort as a whole and in the 5-year RA subgroup (Table 2; for complete table of results, see supplementary table 1, available as supplementary data at *Rheumatology* Online). As expected, due to the strong correlation between ACPA and *HLA-SE*, carriage of *HLA-SE* alleles also strongly associated with erosive disease at 5 years (Table 2).

Only 2 of the 18 SNPs tested showed a trend towards association with the presence of erosions by Year 5. Both SNPs map to the *TRAF1/C5* locus and the minor allele of both markers is associated with susceptibility to RA in multiple populations [23]. The SNP marker rs2900180 (*TRAF1/C5*) was associated, by carriage of the minor allele, with erosive disease by the 5-year follow-up in both the 5-year IP cohort as a whole and the RA subset (Table 2). The other SNP, rs10760130, showed a trend towards association but this did not achieve statistical significance (Table 2). Moderate linkage disequilibrium exists between rs10760130 and rs2900180, $R^2 = 0.67$ [24]. Adjustments for DMARD/steroid treatment did not materially alter these findings (analysis not shown).

Although ACPA status, carriage of *HLA-SE* alleles and carriage of the minor allele of the SNP markers were associated with the presence of erosions by 5 years, only

Table 1 Summary of cohort characteristics

Cohort characteristics	5-year IP cohort ($n = 663$)		5-year RA cohort ($n = 489$)		1-year RA cohort ($n = 761$)	
Age at symptom onset, median (IQR), years	53	(42–63)	55	(44–65)	57	(46–68)
Delay from onset to registration, median (IQR), months	5.2	(2.4–11.0)	5.3	(2.5–11.0)	5.4	(2.6–12.0)
Female, *n* (%)	448	(68)	333	(68)	520	(68)
HAQ score baseline, median (IQR)	0.75	(0.25–1.38)	0.88	(0.25–1.5)	1	(0.5–1.6)
Larsen score Year 1, median (IQR)	–	–	–	–	5	(0, 15)
Erosive disease Year 1, *n* (%)	–	–	–	–	365	(48)
Larsen score Year 5, median (IQR)	5	(0–21)	10	(1–29)	–	–
Erosive disease Year 5, *n* (%)	291	(44)	272	(56)	–	–
Anti-CCP positive, *n* (%)	170	(29)	163	(38)	269	(39)
Satisfy ACR criteria for RA, *n* (%)	489	(74)	–	–	761	(100)

CCP: cyclic citrullinated peptide.

Table 2 Association between prognostic markers and erosive disease

Marker	5-year IP cohort obs.	Erosions at Year 5 OR (95% CI)	5-year RA subgroup obs.	Erosions at Year 5 OR (95% CI)	1−year RA cohort obs.	Erosions at Year 1 OR (95% CI)
Anti-CCP	577		424		682	
Positive	170	9.12 (5.96, 14.00); $P = 5.1e{-}29$	163	6.80 (4.26, 10.85); $P = 2.2e{-}18$	269	5.59 (4.00, 7.83); $P = 9.2e{-}26$
HLA-SE	603		455		693	
Carriage	368	2.17 (1.55, 3.05); $P = 5.7e{-}06$	284	2.59 (1.76, 3.82); $P = 1.2e{-}06$	441	2.12 (1.55, 2.91); $P = 2.4e{-}06$
rs10760130	657		484		750	
One copy	309	1.23 (0.86, 1.78)	223	1.31 (0.86, 1.98)	367	1.63 (1.17, 2.29)
Two copies	143	1.58 (1.03, 2.44)	112	1.47 (0.89, 2.40)	161	1.22 (0.81, 1.84)
Carriage		1.33 (0.95, 1.86); $P = 0.10$		1.36 (0.92, 2.00); $P = 0.12$		1.50 (1.09, 2.05); $P = 0.01$
rs2900180	658		485		753	
One copy	300	1.54 (1.11, 2.15)	222	1.50 (1.02, 2.22)	353	1.58 (1.15, 2.15)
Two copies	87	1.25 (0.76, 2.03)	68	1.10 (0.63, 1.90)	105	1.37 (0.88, 2.15)
Carriage		1.47 (1.07, 2.02); $P = 0.02$		1.40 (0.97, 2.00); $P = 0.08$		1.53 (1.14, 2.05); $P = 0.005$

The comparison group for anti-CCP: anti-CCP-negative patients. The comparison group for the SNP markers: patients who carry two copies of the non-risk allele. Carriage: at least one copy of the risk allele i.e. dominant model. CCP: cyclic citrullinated peptide.

Table 3 Association between prognostic factors and Larsen score in patients with erosive disease

Marker	5-year IP cohort obs.	Larsen score at Year 5 IRR (95% CI)	5-year RA subgroup obs.	Larsen score at Year 5 IRR (95% CI)	1-year RA cohort obs.	Larsen score at Year 1 IRR (95% CI)
Anti-CCP	228		214		265	
Positive	127	1.57 (1.34, 1.84); $P = 5.9e{-}8$	126	1.51 (1.29, 1.78); $P = 1.5e{-}6$	168	1.24 (1.06, 1.45); $P = 0.009$
HLA-SE	244		231		284	
Carriage		1.24 (1.04, 1.47); $P = 0.02$		1.21 (1.01, 1.45); $P = 0.04$		1.18 (0.99, 1.41); $P = 0.06$
rs10760130	262		245		297	
One copy	126	0.97 (0.80, 1.17)	119	0.95 (0.79, 1.15)	158	1.00 (0.84, 1.20)
Two copies	68	0.98 (0.79, 1.22)	63	0.99 (0.80, 1.23)	59	1.00 (0.80, 1.24)
Carriage		0.97 (0.82, 1.16)		0.97 (0.81, 1.16)		1.00 (0.84, 1.18)
rs2900180	263		246		298	1.02 (0.87, 1.20)
One copy	136	0.95 (0.80, 1.13)	126	0.95 (0.80, 1.13)	153	0.92 (0.73, 1.17)
Two copies	36	1.03 (0.81, 1.33)	34	1.05 (0.82, 1.35)	41	1.00 (0.86, 1.17)
Carriage		0.97 (0.83, 1.14)		0.98 (0.83, 1.15)		

The comparison group for anti-CCP: anti-CCP-negative patients. The comparison group for the SNP markers: patients who carry two copies of the non-risk allele. Carriage: at least one copy of the risk allele i.e. dominant model. CCP: cyclic citrullinated peptide.

ACPA positivity and *HLA-SE* carriage were associated with higher Larsen score by Year 5 in both the 5-year IP cohort as a whole and in the 5-year RA subgroup (Table 3). There was no association of the SNP markers rs2900180 and rs10760130 with Larsen score by Year 5 (Table 3).

Radiological erosions by Year 1

As expected, ACPA and *HLA-SE* status also strongly associated with the development of erosions in the 1-year IP cohort (Table 2; for complete table of results, see supplementary table 1, available as supplementary data at *Rheumatology* Online). Both the rs2900180 and rs10760130 *TRAF1/C5* SNPs were associated, by carriage of the minor allele, with erosive disease at Year 1 (Table 2). The odds ratios (ORs) conferred by carriage of the minor allele were higher in the 1-year RA group compared with the 5-year IP cohort as a whole—in keeping with our hypothesis that the 1-year IP cohort represents a more severe group (Table 2). However, this is unlikely to

be an important effect, illustrated by extensive overlap in CIs between Years 1 and 5, and, in addition, the contrary was observed for ACPA positivity (Table 2). For both SNPs, carriage of one copy of the risk allele appeared to confer a higher risk of erosions than carriage of two copies when compared with carriage of no copies. However, there were low numbers of patients with two copies of either risk allele and a substantial overlap in CIs was observed. None of the other SNP markers tested showed association with erosions in this 1-year RA cohort.

Multivariate analysis of genetic markers: ACPA status

Multivariate logistic regression models were used to assess the improvement in predicting erosions in IP patients who carried the risk allele of either rs10760130 or rs2900180, over and above that estimated from ACPA positivity alone. In the 5-year IP cohort, carriage of the risk allele for either rs2900180 [$n = 572$; OR 1.65 (95% CI 1.13, 2.42); $P = 0.01$] or rs10760130 [$n = 571$; OR 1.52 (95% CI 1.00, 2.29); $P = 0.05$] conferred risk of erosions in IP patients following adjustment for ACPA positivity, and effect sizes were similar in the ACPA-negative patients [$n = 404$; OR 1.52 (95% CI 0.98, 2.38); $P = 0.06$] and [$n = 403$; OR 1.42 (95% CI 0.88, 2.29); $P = 0.15$] were compared with the ACPA-positive subgroup [$n = 168$; OR 2.07 (95% CI 0.97, 4.40); $P = 0.06$] and [$n = 168$; OR 1.80 (95% CI 0.82, 3.90); $P = 0.14$] for rs2900180 and rs10760130, respectively (difference in effect between patient stratum $P = 0.50$ for rs2900180 and $P = 0.62$ for rs10760130).

Following adjustment for ACPA positivity, carriage of the risk allele of rs10760130 also predicted erosive disease in the 1-year IP cohort [$n = 672$; OR 1.62 (95% CI 1.13, 2.33); $P = 0.009$]. Importantly, carriage of the minor allele conferred risk of erosions in ACPA-negative patients [$n = 407$; OR 2.30 (95% CI 1.39, 3.80); $P = 0.001$], but not in ACPA-positive patients [$n = 265$; OR 1.00 (95% CI 0.56, 1.79); $P = 0.99$] and this difference was significant ($P = 0.03$). The result was corroborated by receiver operating characteristic analysis in which inclusion of rs10760130 did not improve the diagnostic utility of ACPA positivity (analysis not shown). Similarly, carriage of the risk allele for rs2900180 was predictive of erosions at Year 1 following adjustment for ACPA positivity [$n = 675$; OR 1.48 (95% CI 1.06, 2.08); $P = 0.02$] and conferred risk of erosions in ACPA-negative patients [$n = 408$; OR 1.71 (95% CI 1.11, 2.65); $P = 0.02$], but not ACPA-positive patients [$n = 267$; OR 1.18 (95%CI 0.68, 2.04); $P = 0.6$]. The difference was not significant ($P = 0.3$). Both rs2900180 and rs10760130 were investigated in the context of *HLA-SE* carriage to see if a statistical interaction between the genetic loci existed; however, none was detected (data not shown).

Discussion

Recent large-scale whole-genome and candidate gene association studies have identified a number of SNP markers that reproducibly associate with RA susceptibility, substantially improving our understanding of the genetic component of disease susceptibility. While this is important, it is unlikely to have an immediate clinical impact unless these markers also associate with prognosis or treatment response.

We hypothesized that genetic susceptibility markers may also be important predictors of outcome. In the current study, the SNP markers rs10760130 and rs2900180 (*TRAF1/C5*) were associated with erosive disease (Table 2), but not with higher Larsen scores at either Year 1 or Year 5 in patients with erosive disease (i.e. Larsen score of $\geqslant 2$ in at least one joint; Table 3). In contrast, ACPA positivity and carriage of *HLA-SE* were associated with the presence of erosions, Larsen score and with the number of eroded joints (data not shown). This suggests that, unlike ACPA status and carriage of *HLA-SE*, the *TRAF1/C5* locus may predict those patients who are more likely to develop erosive disease, but not the severity or extent of erosions. It should be noted that in this investigation, 18 SNPs mapping to 14 loci were assessed for association with disease outcome resulting in multiple testing and the consequent potential of generating false positive results. No correction has been applied, so as not to preclude the identification of small putative effects, but, if it had, neither of the SNP markers would have achieved statistical significance at the corrected threshold ($P < 0.003$). However, the association of the *TRAF1/C5* locus with erosive disease has previously been reported (with the SNP rs10818488; in $R^2 = 1$ with rs10760130) [25]. Hence, the current findings provide further support that this locus is associated with disease outcome. In the current study, the effect seen at the rs2900180 SNP locus in patients homozygous for the risk allele was observed to be lower than that observed for heterozygotes, albeit with considerable overlap in the CIs. Although the effect at this locus is consistent with a dominant model, this pattern perhaps reflects the small number of observations in the homozygous patient group (Table 2). However, validation of association of the locus with disease severity is required in larger, independent data sets.

Logistic regression analyses found that the *TRAF1/C5* genetic markers (rs10760130 and rs2900180) predict erosive disease independent of ACPA status; indeed, the effect appears stronger in ACPA-negative patients at Year 1. This could be more helpful clinically as this subgroup is often not treated as intensively as ACPA-positive patients. The presence of genetic risk alleles may highlight the potential for erosive damage and prompt clinicians to consider earlier, more aggressive treatment regimes. The sensitivity (80% for rs10760130 and 66% for rs2900180) and specificity (36% for rs10760130 and 46% for rs2900180) of genotyping at either locus, in ACPA-negative patients, to predict the development of erosions by Year 1 is too low to be clinically useful at the current time but, as more markers of severity are identified, this may become viable in the future.

Failure to detect associations with the other susceptibility loci tested may reflect inadequate power. Assuming a 50% increase in risk of developing erosions, the study had 14–95% power to detect the effect of carriage of a susceptibility allele at eight of the loci tested [rs5029937 (14%), rs6822844 (64%), rs4750316 (80%), rs7574865 (88%), rs4810485 (90%), rs6920220 (91%), rs13207033 (94%) and rs6897932 (95%)] at Year 5 in IP patients, at the 5% significance level. There was >95% power for the remaining loci. The study therefore had limited power to detect modest effects due to the limited sample size, particularly for some of the subgroups analysed and may, therefore, represent false negative findings. For many of these regions, either multiple polymorphisms have been associated with susceptibility and/or the true causal variants have not yet been identified resulting in a further loss in power to identify potential modest severity effects. National and international collaboration is likely to be required to establish large enough cohorts to fully explore genetic predictors of outcome. Alternatively, genetic susceptibility markers may differ from those contributing to disease severity. If this is true, there is a need for a separate well-powered within-cohort genome-wide association study to identify genetic markers of outcome and to improve the predictive models over and above the presence of ACPA positivity alone.

These data add more weight to the case for routine screening for ACPA in clinical practice in order to identify those patients who are likely to have a poor prognosis in terms of radiographic erosions. These data also add to the evidence that SNP markers within the *TRAF1/C5* locus are associated with the risk of erosive disease and suggest that this effect is independent of ACPA.

Rheumatology key messages

- ACPA positivity remains the strongest predictor of radiological outcome in patients with IP.
- We provide evidence that the *TRAF1/C5* locus is associated with erosive disease in IP patients.
- The *TRAF1/C5* locus is associated with excess risk of erosive disease independent of ACPA status.

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