PADI4 genotype is not associated with rheumatoid arthritis in a large UK Caucasian population

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ABSTRACT

Background Polymorphisms of the peptidylarginine deiminase type 4 (*PADI4*) gene confer susceptibility to rheumatoid arthritis (RA) in East Asian people. However, studies in European populations have produced conflicting results. This study explored the association of the *PADI4* genotype with RA in a large UK Caucasian population.

Methods The PADI4_94 (rs2240340) single nucleotide polymorphism (SNP) was directly genotyped in a cohort of unrelated UK Caucasian patients with RA (n=3732) and population controls (n=3039). Imputed data from the Wellcome Trust Case Control Consortium (WTCCC) was used to investigate the association of PADI4_94 with RA in an independent group of RA cases (n=1859) and controls (n=10 599). A further 56 SNPs spanning the *PADI4* gene were investigated for association with RA using data from the WTCCC study.

Results The PADI4_94 genotype was not associated with RA in either the present cohort or the WTCCC cohort. Combined analysis of all the cases of RA (n=5591) and controls (n=13 638) gave an overall OR of 1.01 (95% CI 0.96 to 1.05, p=0.72). No association with anti-CCP antibodies and no interaction with either shared epitope or *PTPN22* was detected. No evidence for association with RA was identified for any of the *PADI4* SNPs investigated. Meta-analysis of previously published studies and our data confirmed no significant association between the PADI4_94 genotype and RA in people of European descent (OR 1.06, 95% CI 0.99 to 1.13, p=0.12).

Conclusion In the largest study performed to date, the *PADI4* genotype was not a significant risk factor for RA in people of European ancestry, in contrast to Asian populations.

INTRODUCTION

Rheumatoid arthritis (RA) is a complex autoimmune disease in which genetic and environmental factors contribute to the pathogenesis. Around 60% of the risk of RA is genetic, a third of which is accounted for by *HLA-DRB1*.[1] Numerous polymorphisms outside the HLA region have recently been confirmed as RA susceptibility loci in Caucasians, but fewer have been tested across different ethnic populations and the question of whether racial heterogeneity exists—that is, whether possession of a particular allele may confer disease susceptibility in one ethnic group but not another—is contentious.[2–4] The peptidylarginine deiminase 4 (*PADI4*) gene is of particular interest as it has been tested in Asian, European and North American populations and its relative effect in relation to RA susceptibility across these groups remains controversial.[5–13]

The *PADI4* gene encodes the type 4 peptidylarginine deiminase enzyme which catalyses the post-translational modification of arginine to citrulline, generating citrullinated proteins. Antibodies to these peptides are highly specific for RA and often predate the development of disease, suggesting a critical role in the pathogenesis of RA. *PADI4* therefore represents an attractive RA candidate gene and was first reported to be associated with RA in a Japanese population in 2003.[5] This association has been consistently replicated in East Asian populations[6 11 12]; however findings in cohorts of European ancestry have been inconsistent. Studies in Spanish, Swedish and UK populations reported no evidence for association of *PADI4* with RA.[7 9 10] Conversely, *PADI4* was found to be associated with RA in North American and German populations and two published meta-analyses suggested that *PADI4* polymorphisms do confer susceptibility to RA in those of European descent, albeit to a lesser degree than in Asian subjects.[10 13–15] Consequently, it was hypothesised that these European studies were underpowered to detect a true but modest genetic effect. The present study was designed to address this issue by exploring the association between the *PADI4* genotype and RA in a large UK population.

MATERIALS AND METHODS

Study design

The PADI4_94 single nucleotide polymorphism (SNP) (rs2240340) was selected for investigation as it has the strongest evidence for association with RA in Asians and Caucasians.[5 12 14 15] It was genotyped in an independent UK Caucasian population of 3732 patients with RA and 3039 controls (see online supplement). In addition, imputed genotypes for the PADI4_94 SNP were compared between 1859 patients with RA and 2935 controls from the Wellcome Trust Case Control Consortium (WTCCC) study.[16] Where linkage disequilibrium (LD) is high and confidence scores for imputed genotypes exceed 95%, the accuracy of imputation in predicting actual genotype counts exceeds 98.4%.[17] An expanded reference group of 10 599 subjects was created by using imputed genotype data for PADI4_94 from the four non-autoimmune disease case subjects (hypertension, coronary artery disease, type 2 diabetes and bipolar disorder) genotyped as part of the WTCCC study and combining this with the genotype data from

the healthy controls. The data from the present cohort and the WTCCC study were combined to provide a robust estimate of effect size for this SNP in the UK population, giving a combined sample size of 5591 cases of RA and 13 638 controls. In addition, imputed genotype data for the original WTCCC cohort (1860 cases of RA, 2938 controls) were used to investigate other SNPs spanning the *PADI4* gene for evidence of association with RA.

Analysis of data

Allele and genotype frequencies were compared between patients with RA and controls using the χ^2 test for trend implemented in PLINK. The threshold for significance was defined at $p<0.05$.

Meta-analysis

Meta-analysis of the results together with previous studies investigating association of PADI4_94 with RA in populations of European ancestry was performed (see online supplement). A random effects model was used and between-study heterogeneity assessed using the Cochran Q-statistic ($p<0.1$ considered significant).

Interaction analysis

Data were available for shared epitope (SE) and the *PTPN22* R620W SNP (rs2476601) in the current cohort. The risk of RA associated with carriage of PADI4_94, PTPN22 and SE risk alleles (1 or 2 copies) alone and in combination was calculated using logistic regression. Interaction effects were quantified by calculating the attributable proportion,[18] which assesses the proportion of the incidence that is due to interaction (ie, beyond the additive effects of each independent variant). There is evidence of biological interaction if the attributable proportion is not equal to 0.

Power

The present cohort had >80% power to detect the published OR of 1.13 at the 5% significance level ($\alpha=0.05$) with a risk allele frequency of 0.42.[15]

RESULTS

The genotyping success rate was >97% in both cases and controls. In this independent cohort of 3732 cases of RA and 3039 controls, no significant difference in PADI_94 allele or genotype frequencies was detected (table 1).

WTCCC cohort

Imputed minor allele frequencies for PADI_94 in the WTCCC cohort were similar to those previously reported in European populations and to those observed in the current study. No association between PADI4_94 genotype and RA was observed (table 1).

Combined analysis

Combined analysis of the current and WTCCC cohorts showed no evidence for association between PADI4_94 genotype and RA. No significant heterogeneity between these two cohorts was detected ($p_{het}=0.43$, $I^2=0\%$) and meta-analysis under a random effects model yielded a similar overall OR of 1.00 (95% CI 0.95 to 1.05). There was no significant difference in genotype distribution between the WTCCC patients with non-autoimmune disease, the original WTCCC controls and the current controls ($p=0.20$, $\chi^2=6.0$). Excluding the WTCCC patients with non-autoimmune disease from the analysis did not affect the outcome (OR 1.02 (95% CI 0.97 to 1.08)).

Studies in Asian populations have shown that PADI4_94 exerts an allele dose-dependent effect in RA susceptibility, with the greatest effect being seen when comparing minor allele homozygotes (2/2) with major allele homozygotes (1/1).[5 12] In contrast, we found no evidence for association in any of the genotypic models tested (table 1).

Stratification

Stratification analysis creates more homogenous subsets of patients and thus may increase the power to detect association despite loss of sample size. Phenotype data were available for a proportion of patients within the current cohort. Stratification by autoantibody status, gender and SE revealed no evidence for association in any of the subgroups tested (table 2).

Meta-analysis

Five eligible studies investigating the PADI4_94 SNP for association with RA in Caucasian populations were identified.[8–10 13 19] Eight separate comparisons were available for the allelic model (minor allele 2 vs common allele 1) and seven for the genotypic model (1/2 vs 1/1 and 2/2 vs 1/1). No significant association between PADI4_94 and RA was detected for any of the models tested (figure 1). The pooled OR for allele 2 vs allele 1 was 1.06 (95% CI 0.99 to 1.13, p=0.12). The OR for 1/2 vs 1/1 was 1.04 (95% CI 0.92 to 1.17, p=0.53) and for 2/2 vs 1/1 was 1.07 (95% CI0.96 to1.19, p=0.20). Significant between-study heterogeneity was noted ($p_{het}=0.06$, $I^2=49.1\%$). Analysis restricted to European cohorts (ie, excluding North American cohorts whose genetic background may be more ethnically diverse) gave an OR

Table 1 PADI4_94 (rs2240340) genotypes in current and WTCCC cohorts

	RA cases*				Controls*				Allele 2 vs allele 1 OR (95% CI)	p Trend	12 vs 11 OR (95% CI)	22 vs 11 OR (95% CI)
	11	12	22	MAF	11	12	22	MAF				
Current cohort	1238 (33.2)	1841 (49.3)	653 (17.5)	0.42	1018 (33.5)	1508 (49.6)	513 (16.9)	0.42	1.02 (0.95 to 1.09)	0.58	1.00 (0.90 to 1.12)	1.05 (0.91 to 1.20)
WTCCC	665 (35.8)	860 (48.3)	334 (18.0)	0.41	1031 (35.1)	1434 (48.9)	470 (16.0)	0.40	1.03 (0.95 to 1.12)	0.54	0.93 (0.82 to 1.06)	1.10 (0.93 to 1.30)
WTCCC plus non-autoimmune controls	665 (35.8)	860 (48.3)	334 (18.0)	0.41	3614 (34.1)	5154 (48.6)	1831 (17.3)	0.42	0.98 (0.91 to 1.05)	0.59	0.91 (0.81 to 1.01)	0.99 (0.86 to 1.14)
Combined analysis	1903 (34.0)	2701 (48.3)	987 (17.7)	0.42	4632 (34.0)	6662 (48.8)	2344 (17.2)	0.42	1.01 (0.96 to 1.05)	0.72	0.99 (0.92 to 1.06)	1.02 (0.94 to 1.12)

*Data shown as number (%).
1, major (common) allele; 2, minor (rare) allele; MAF, minor allele frequency; WTCCC, Wellcome Trust Case Control Consortium.

of 1.01 (95% CI 0.96 to 1.07) with no significant heterogeneity (p_{het}=0.31, I^2=16.8%).

Interaction analysis

Significant interaction between SE and *PTPN22* was detected in anti-CCP positive RA, consistent with previous reports (tables 3 and 4).[20] In contrast, there was no significant interaction between PADI4_94 and either *PTPN22* or SE. In a model containing all three factors, the highest ORs were seen with possession of SE alleles in conjunction with the *PTPN22* risk allele, regardless of the presence or absence of the PADI4_94 putative risk allele (data not shown).

Table 2 PADI4_94 genotype in current cohort stratified by autoantibody status, carriage of SE, presence of erosions and gender

	Cases*				Controls*					
	11	12	22	Total	11	12	22	Total	Allele 2 vs 1 OR (95% CI)	p Trend
CCP +ve vs all controls	498 (33.2)	722 (48.2)	279 (18.6)	1499	1018 (33.5)	1508 (49.6)	513 (16.9)	3039	1.04 (0.95 to 1.14)	0.36
CCP –ve vs all controls	241 (34.4)	347 (49.5)	113 (16.1)	701	1018 (33.5)	1508 (49.6)	513 (16.9)	3039	0.97 (0.86 to 1.09)	0.57
CCP +ve vs CCP –ve	498 (33.2)	722 (48.2)	279 (18.6)	1499	241 (34.4)	347 (49.5)	113 (16.1)	701	1.08 (0.95 to 1.23)	0.25
RF +ve vs all controls	849 (33.4)	1250 (49.1)	444 (17.5)	2543	1018 (33.5)	1508 (49.6)	513 (16.9)	3039	1.01 (0.94 to 1.09)	0.71
RF –ve vs all controls	328 (34.2)	467 (48.7)	165 (17.2)	960	1018 (33.5)	1508 (49.6)	513 (16.9)	3039	0.99 (0.89 to 1.10)	0.89
Erosions	394 (33.8)	576 (49.4)	195 (16.8)	1165	1018 (33.5)	1508 (49.6)	513 (16.9)	3039	0.99 (0.9 to 1.09)	0.85
No erosions	183 (33.0)	270 (48.8)	101 (18.2)	554	1018 (33.5)	1508 (49.6)	513 (16.9)	3039	1.04 (0.91 to 1.18)	0.57
SE +ve (1 or 2 copies)	747 (33.3)	1093 (48.6)	407 (18.1)	2247	214 (36.2)	276 (46.6)	102 (17.2)	592	1.08 (0.95 to 1.23)	0.24
SE –ve (0 copies)	244 (32.7)	373 (49.9)	130 (17.4)	747	231 (32.6)	359 (50.6)	119 (16.8)	709	1.01 (0.87 to 1.17)	0.88
Men	334 (32.3)	524 (50.7)	176 (17.0)	1034	304 (32.6)	471 (50.5)	158 (16.9)	933	1.01 (0.89 to 1.15)	0.91
Women	896 (33.6)	1294 (48.6)	474 (17.8)	2664	657 (33.9)	964 (49.8)	315 (16.3)	1936	1.04 (0.95 to 1.13)	0.38

*Data shown as number (%).
1, major (common) allele; 2, minor (rare) allele; RF, rheumatoid factor; SE, shared epitope.

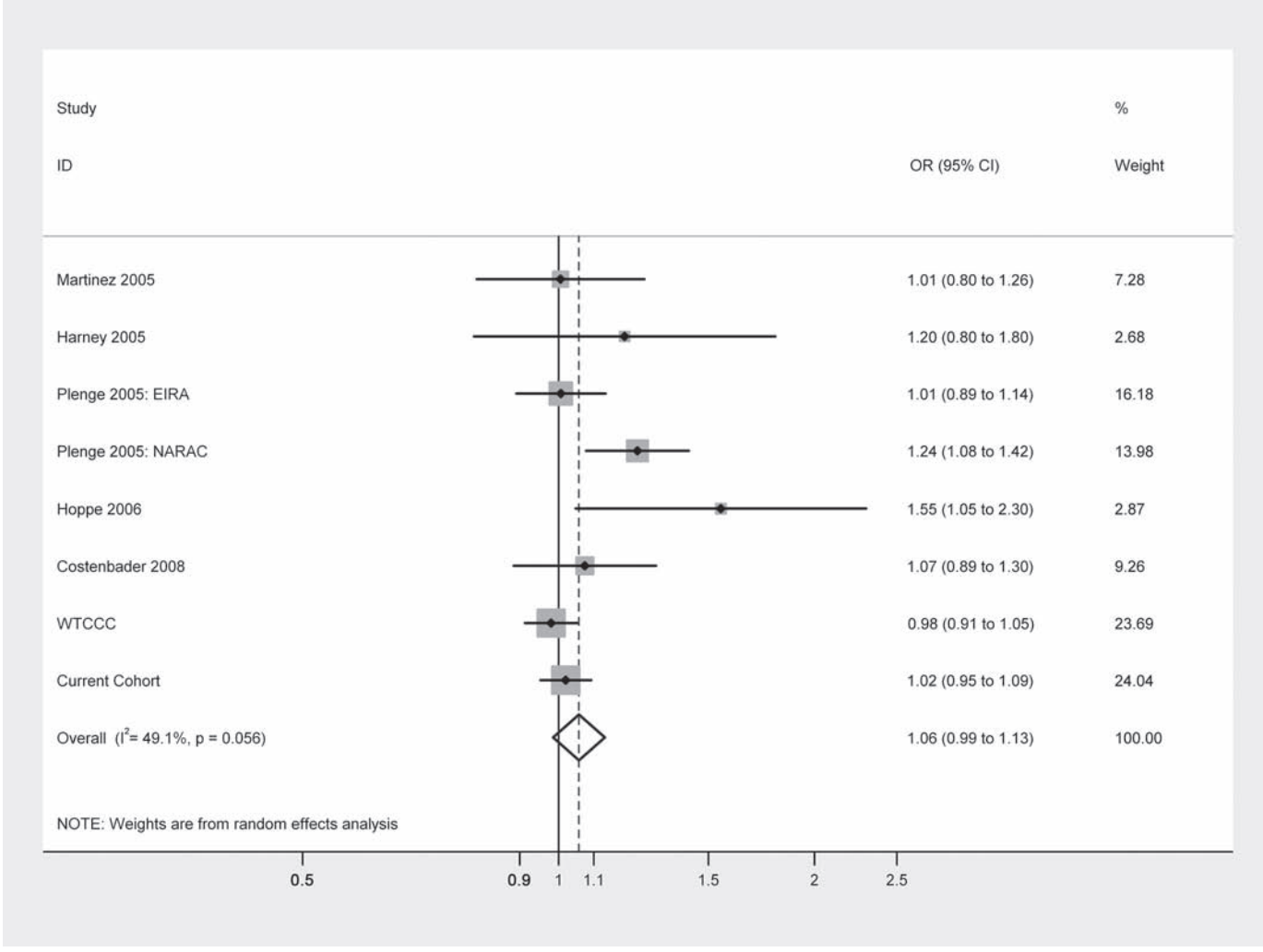

Figure 1 Meta-analysis of PADI4_94 in populations of European descent. Odds ratio (OR), minor allele (2) vs common allele (1). Weight expressed as percentage.

Table 3 Details of studies included in meta-analysis and subsequent analysis of SE, PTN22 and PADI4_94 risk allele combinations

Study	Population	Sample size		PADI4_94 allele 2 vs 1	
		RA cases	Controls	OR (95% CI)	p Value
Martinez (2005)[9]	Spain	248	394	1.01 (0.80 to 1.26)	1.00
Harney (2005)[8]	UK	100	94	1.20 (0.80 to 1.80)	0.41
Plenge (2005): EIRA[10]	Sweden	1498	858	1.01 (0.89 to 1.14)	0.93
Plenge (2005): NARAC[10]	North America	895	748	1.24 (1.06 to 1.42)	0.003
Hoppe (2006)[13]	German	102	102	1.55 (1.05 to 2.30)	0.04
Costenbader (2008)[19]	North America	430	426	1.07 (0.89 to 1.30)	0.49
WTCCC	UK	1859	10599	0.98 (0.91 to 1.05)	0.58
Current cohort	UK	3732	3039	1.02 (0.95 to 1.09)	0.72

EIRA, Epidemiological Investigation of Rheumatoid Arthritis; NARAC, North American Rheumatoid Arthritis Consortium; SE, shared epitope; WTCCC, Wellcome Trust Case Control Consortium.

Table 4 Odds ratios for developing rheumatoid arthritis (RA) according to presence or absence of SE, PTPN22 R620W and PADI4_94 risk alleles: allele 2 (minor allele) vs allele 1 (common allele)

Presence of risk allele		All cases			CCP positive cases			CCP negative cases		
PADI4_94	PTPN22	Case:control	OR (95% CI)	AP (CI)	Case:control	OR (95% CI)	AP (CI)	Case:control	OR (95% CI)	AP (CI)
None	None	876:810	Referent	0.0 (–0.4 to 0.4)	340:810	Referent	0.0 (–0.3 to 0.3)	182:810	Referent	0.0 (–0.4 to 0.4)
Present	None	1771:1618	1.0 (0.9 to 1.1)		680:1618	1.0 (0.9 to 1.2)		349:1618	1.0 (0.8 to 1.2)	
None	Present	334:191	**1.6 (1.3 to 2.0)**		146:191	**1.8 (1.4 to 2.3)**		51:191	1.2 (0.8 to 1.7)	
Present	Present	679:386	**1.6 (1.4 to 1.9)**		300:386	**1.9 (1.5 to 2.3)**		102:386	1.2 (0.9 to 1.5)	
PADI4_94	**SE**									
None	None	244:231	Referent	0.1 (–0.1 to 0.3)	62:231	Referent	0.1 (–0.1 to 0.3)	94:231	Referent	0.2 (–0.1 to 0.5)
Present	None	503:478	1.0 (0.8 to 1.2)		154:478	1.2 (0.9 to 1.7)		162:478	0.8 (0.6 to 1.1)	
None	Present	747:214	**3.3 (2.6 to 4.2)**		382:214	**6.7 (4.8 to 9.2)**		118:214	**1.4 (1.0 to 1.9)**	
Present	Present	1500:378	**3.8 (3.0 to 4.6)**		747:378	**7.4 (5.4 to 10.0)**		240:378	**1.6 (1.2 to 2.1)**	
PTPN22	**SE**									
None	None	553:563	Referent	0.3 (0.1 to 0.5)	145:563	Referent	**0.4 (0.1 to 0.6)**	204:563	Referent	0.2 (–0.1 to 0.5)
Present	None	200:141	**1.4 (1.1 to 1.8)**		71:141	**2.0 (0.7 to 5.7)**		52:141	1.0 (0.7 to 1.5)	
None	Present	1610:474	**3.5 (3.0 to 4.0)**		779:474	**6.4 (5.1 to 7.9)**		270:474	**1.6 (1.3 to 2.0)**	
Present	Present	626:116	**5.5 (4.4 to 6.9)**		347:116	**11.6 (8.8 to 15.3)**		87:116	**2.1 (1.5 to 2.9)**	

Present, 1 or 2 copies of SE, PTPN22 R620W risk allele or PADI4_94 putative risk allele. Significant results in bold.
None, no copies.
AP, attributable proportion; CCP, cyclic citrullinated peptide; SE, shared epitope.

Further PADI4 SNPs

Imputed genotype data were available for 1860 cases of RA and 2938 controls from the WTCCC study. A further 56 SNPs spanning the *PADI4* gene with imputation confidence scores of over 99% were identified. No evidence for association with RA was detected for any of these SNPs (see table 1 in online supplement). Importantly, PADI4_89 and PADI4_90, which have previously been reported to be associated with RA in Caucasians, were not associated in this UK cohort (see table 2 in online supplement).[13 21]

DISCUSSION

In the largest study performed to date, we found no evidence for association between the PADI4_94 SNP and RA in a combined sample of over 19 000 UK subjects. The results were consistent across two large independent populations, lending weight to these findings.

This contrasts with the convincing evidence that *PADI4* is an RA susceptibility gene in East Asian subjects.[5 6 11 12] The strongest association is seen with PADI4_94, with an estimated OR of 1.31, making it the major genetic risk factor outside the HLA region in this group.[12 14 15] Consistent with our findings, several other groups have failed to find an association between PADI4_94 and RA in populations of European ancestry. However, meta-analyses of published data in Caucasians demonstrated evidence for association with a summary OR of 1.13.[14 15] For a study to have 80% power to detect an OR of 1.13 at p<0.05, more than 4200 subjects would be required. All previous studies have been underpowered to detect an OR of this level, conceivably accounting for the frequent failure to replicate the association. However, these meta-analyses were based on comparatively limited data (pooled total of 2950 RA cases and 2300 controls) and findings may have been influenced by publication bias and heterogeneity between studies. The present study circumvents these problems by using two independent cohorts, each with more than 80% power to detect the published OR, thus minimising the chance of a type II error. Furthermore, there was no significant difference when comparing minor allele homozygotes with major allele homozygotes (OR 1.02), which is where the greatest effect is seen in Asian populations (OR 1.73).[12] Our findings suggest that previous reported associations between PADI4_94 and RA in European populations are false-positive results.

The differential effect of the PADI4_94 SNP in populations of Asian and European descent is unusual as, although the frequency of complex disease-associated polymorphisms may vary across ethnic groups, their genetic effects are usually consistent.[2] There are several plausible explanations for this discrepancy.

First, linkage disequilibrium varies between races, so PADI4_94 may be in linkage disequilibrium with the true disease-associated allele in Asian but not Caucasian populations. However, *PADI4* SNP and haplotype frequencies are similar in the two populations.[7] Second, it is possible that different *PADI4* polymorphisms may be associated with RA in Caucasians. However, this would be unlikely given that we investigated numerous SNPs spanning the *PADI4* gene within the WTCCC cohort and found no evidence for association across the locus as a whole. Third, the biological effect of PADI4_94 variants may be modulated by environmental exposures such as smoking or interactions with other genes which may differ between races. The *PTPN22* R620W variant is a potential candidate for introducing variation via gene–gene interaction as it is a major risk factor for RA in Caucasians but has not been detected in Japanese populations. However, we found no interaction between PADI4_94 and *PTPN22* in this study. Alternatively, it may be that *PADI4* is associated only with a subgroup of patients with RA. Hoppe *et al* recently suggested that the association between *PADI4* genotype and RA may be restricted to patients with more severe disease.[22] It is unlikely, however, that this would account for the differences observed as the cohorts tested in the WTCCC and current studies were comparable with the Japanese cohort in terms of disease characteristics. Moreover, *PADI4* genotype was not associated with the presence of cyclic citrullinated peptide (CCP) antibody, rheumatoid factor or erosions in this study, and we have previously found no relationship between *PADI4* genotype and disease severity in UK patients with early inflammatory arthritis followed prospectively.[23]

Finally, the disparity in genetic effect may reflect genuine differences in pathogenic processes between European and Asian populations. The mechanism by which the *PADI4* genotype may influence RA susceptibility has not yet been elucidated. Suzuki *et al* showed that the *PADI4* susceptibility haplotype had significantly increased mRNA stability compared with the non-susceptibility haplotype. In theory this could result in increased PAD4 enzyme, with consequently increased protein citrullination which may break immune tolerance leading to production of anti-citrullinated peptide antibodies (ACPA) and disease.[5] They went on to demonstrate an association between homozygosity for the *PADI4* susceptibility haplotype and the presence of ACPA. However, we and many others have failed to find any link between *PADI4* genotype and presence of anti-CCP antibodies, drawing this hypothesis into question.[8 10 23–25] Furthermore, given that individuals carrying SE alleles may be predisposed to mount an immune response to citrullinated peptides, the absence of a significant interaction between PADI4_94 and SE in this study is of relevance.[26] We did confirm the previously reported interaction between *PTPN22* and SE, supporting the validity of our data.[20] In a Korean cohort, *PADI4* and SE had additive effects with regard to the risk of RA, although no significant interaction was reported.[11] It would be interesting to investigate this further in Asian populations as distribution of HLA subtypes varies across races and it has been suggested that this could lead to differential modulation of the genetic effects of *PADI4*.[8 11]

In conclusion, in contrast to Asian populations, the *PADI4* genotype is not a significant risk factor for RA in people of European descent. Identification of biological mechanisms responsible for this disparity may yield novel insights into the pathogenic processes underpinning rheumatoid disease.

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Competing interests None.

Ethics approval This study was conducted with the approval of the North West Research ethics committee (MREC 99/9/84).

Membership of the BIRAC Consortium and YEAR Consortium is shown in the online supplement.

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Corrections

The department of one of the authors who co-authored all of the below papers has found that the affiliations were not correct. The correct affiliations for Professor P Emery, for all of the below articles, are: [1]Section of Musculoskeletal Disease, Leeds Institute of Molecular Medicine, University of Leeds; [2]NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals Trust, Leeds, UK.

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