

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

Marian L Burr,¹ Haris Naseem,¹ Anne Hinks,¹ Steve Eyre,¹ Laura J Gibbons,¹ John Bowes,¹ Anthony G Wilson,² James Maxwell,² Ann W Morgan,³ Paul Emery,³ Sophia Steer,⁴ Lynne Hocking,⁵ David M Reid,⁵ Paul Wordsworth,⁶ Pille Harrison,⁶ Wendy Thomson,¹ Jane Worthington,¹ BIRAC Consortium,⁷ YEAR Consortium,⁸ Anne Barton¹

► Additional data (supplementary tables) are published online only at <http://ard.bmj.com/content/vol69/issue4>

¹arc-Epidemiology Unit, University of Manchester, Manchester, UK

²School of Medicine and Biomedical Sciences, University of Sheffield, Sheffield, UK

³Section of Musculoskeletal Disease, Leeds Institute of Molecular Medicine, University of Leeds, UK

⁴Clinical and Academic Rheumatology, King's College Hospital NHS Foundation Trust, London, UK

⁵Bone Research Group, Department of Medicine and Therapeutics, University of Aberdeen, UK

⁶University of Oxford Institute of Musculoskeletal Sciences, Botnar Research Centre, Oxford, UK

⁷BIRAC Consortium

⁸YEAR Consortium

Correspondence to

Dr Anne Barton, arc-Epidemiology Unit, Stopford Building, Oxford Road, University of Manchester, Manchester M13 9PT, UK; anne.barton@manchester.ac.uk

Accepted 10 May 2009

Published Online First 25 May 2009

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 peptidyl-arginine 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



This paper is freely available online under the BMJ Journals unlocked scheme, see <http://ard.bmj.com/info/unlocked.dtl>

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 *PADI4_94* allele or genotype frequencies was detected (table 1).

WTCCC cohort

Imputed minor allele frequencies for *PADI4_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 ($p_{\text{het}} = 0.43$, $I^2 = 0\%$) 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% CI 0.96 to 1.19, $p = 0.20$). Significant between-study heterogeneity was noted ($p_{\text{het}} = 0.06$, $I^2 = 49.1\%$). 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*				Allele 2 vs 1 OR (95% CI)	p Trend
	11	12	22	Total	11	12	22	Total		
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.

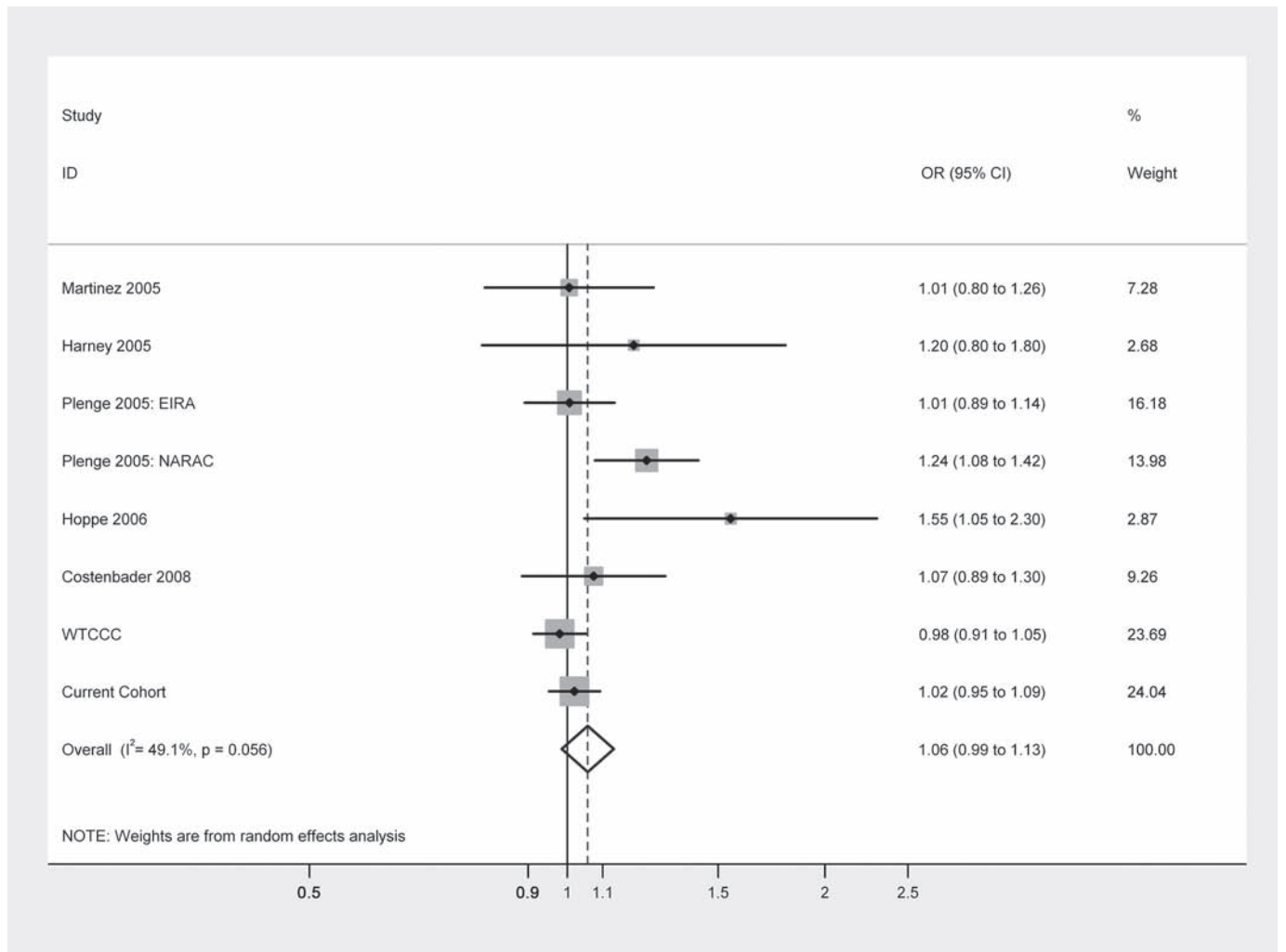


Figure 1 Meta-analysis of *PADI4_94* in populations of European descent. Odds ratio (OR), minor allele (2) vs common allele (1). Weight expressed as percentage.

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.

Acknowledgements The authors thank the Arthritis Research Campaign for their support (arc grant reference number 17552), the Wellcome Trust Case Control Consortium (WTCCC) for providing the genotype data included and acknowledge support from the Manchester Biomedical Research Centre.

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.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. MacGregor AJ, Snieder H, Rigby AS, *et al*. Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. *Arthritis Rheum* 2000;**43**:30–7.
2. Ioannidis JP, Ntzani EE, Trikalinos TA. 'Racial' differences in genetic effects for complex diseases. *Nat Genet* 2004;**36**:1312–18.
3. Barton A, Thomson W, Ke X, *et al*. Rheumatoid arthritis susceptibility loci at chromosomes 10p15, 12q13 and 22q13. *Nat Genet* 2008;**40**:1156–9.
4. Raychaudhuri S, Remmers EF, Lee AT, *et al*. Common variants at CD40 and other loci confer risk of rheumatoid arthritis. *Nat Genet* 2008;**40**:1216–23.
5. Suzuki A, Yamada R, Chang X, *et al*. Functional haplotypes of PADI4, encoding citrullinating enzyme peptidylarginine deiminase 4, are associated with rheumatoid arthritis. *Nat Genet* 2003;**34**:395–402.
6. Ikari K, Kuwahara M, Nakamura T, *et al*. Association between PADI4 and rheumatoid arthritis: a replication study. *Arthritis Rheum* 2005;**52**:3054–7.
7. Barton A, Bowes J, Eyre S, *et al*. A functional haplotype of the PADI4 gene associated with rheumatoid arthritis in a Japanese population is not associated in a United Kingdom population. *Arthritis Rheum* 2004;**50**:1117–21.
8. Harney SM, Meisel C, Sims AM, *et al*. Genetic and genomic studies of PADI4 in rheumatoid arthritis. *Rheumatology (Oxford)* 2005;**44**:869–72.
9. Martinez A, Valdivia A, Pascual-Salcedo D, *et al*. PADI4 polymorphisms are not associated with rheumatoid arthritis in the Spanish population. *Rheumatology (Oxford)* 2005;**44**:1263–6.
10. Plenge RM, Padyukov L, Remmers EF, *et al*. Replication of putative candidate-gene associations with rheumatoid arthritis in >4,000 samples from North America and Sweden: association of susceptibility with PTPN22, CTLA4, and PADI4. *Am J Hum Genet* 2005;**77**:1044–60.
11. Kang CP, Lee HS, Ju H, *et al*. A functional haplotype of the PADI4 gene associated with increased rheumatoid arthritis susceptibility in Koreans. *Arthritis Rheum* 2006;**54**:90–6.
12. Takata Y, Inoue H, Sato A, *et al*. Replication of reported genetic associations of PADI4, FCRL3, SLC22A4 and RUNX1 genes with rheumatoid arthritis: results of an independent Japanese population and evidence from meta-analysis of East Asian studies. *J Hum Genet* 2008;**53**:163–73.
13. Hoppe B, Häupl T, Gruber R, *et al*. Detailed analysis of the variability of peptidylarginine deiminase type 4 in German patients with rheumatoid arthritis: a case-control study. *Arthritis Res Ther* 2006;**8**:R34.
14. Iwamoto T, Ikari K, Nakamura T, *et al*. Association between PADI4 and rheumatoid arthritis: a meta-analysis. *Rheumatology (Oxford)* 2006;**45**:804–7.
15. Lee YH, Rho YH, Choi SJ, *et al*. PADI4 polymorphisms and rheumatoid arthritis susceptibility: a meta-analysis. *Rheumatol Int* 2007;**27**:827–33.
16. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 2007;**447**:661–78.
17. Marchini J, Howie B, Myers S, *et al*. A new multipoint method for genome-wide association studies by imputation of genotypes. *Nat Genet* 2007;**39**:906–13.
18. Andersson T, Alfredsson L, Källberg H, *et al*. Calculating measures of biological interaction. *Eur J Epidemiol* 2005;**20**:575–9.
19. Costenbader KH, Chang SC, De Vivo I, *et al*. Genetic polymorphisms in PTPN22, PADI-4, and CTLA-4 and risk for rheumatoid arthritis in two longitudinal cohort studies: evidence of gene-environment interactions with heavy cigarette smoking. *Arthritis Res Ther* 2008;**10**:R52.
20. Kallberg H, Padyukov L, Plenge RM, *et al*. Gene-gene and gene-environment interactions involving HLA-DRB1, PTPN22, and smoking in two subsets of rheumatoid arthritis. *Am J Hum Genet* 2007;**80**:867–75.
21. Gandjbakhch F, Fajardy I, Ferre B, *et al*. A functional haplotype of PADI4 gene in rheumatoid arthritis: positive correlation in a French population. *J Rheumatol* 2009;**36**:881–6.
22. Hoppe B, Häupl T, Egerer K, *et al*. Influence of peptidylarginine deiminase type 4 genotype and shared epitope on clinical characteristics and autoantibody profile of rheumatoid arthritis. *Ann Rheum Dis* 2009;**68**:898–903.
23. Barton A, Bowes J, Eyre S, *et al*. Investigation of polymorphisms in the PADI4 gene in determining severity of inflammatory polyarthritis. *Ann Rheum Dis* 2005;**64**:1311–5.
24. Poór G, Nagy ZB, Schmidt Z, *et al*. Genetic background of anticyclic citrullinated peptide autoantibody production in Hungarian patients with rheumatoid arthritis. *Ann N Y Acad Sci* 2007;**1110**:23–32.
25. Harris ML, Darrach E, Lam GK, *et al*. Association of autoimmunity to peptidyl arginine deiminase type 4 with genotype and disease severity in rheumatoid arthritis. *Arthritis Rheum* 2008;**58**:1958–67.
26. Hill JA, Southwood S, Sette A, *et al*. Cutting edge: the conversion of arginine to citrulline allows for a high-affinity peptide interaction with the rheumatoid arthritis-associated HLA-DRB1*0401 MHC class II molecule. *J Immunol* 2003;**171**:538–41.

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: ¹Section of Musculoskeletal Disease, Leeds Institute of Molecular Medicine, University of Leeds; ²NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals Trust, Leeds, UK.

1. **Keystone E**, Emery P, Peterfy CG, *et al.* Rituximab inhibits structural joint damage in patients with rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitor therapies. *Ann Rheum Dis* 2009;**68**:216–21.
2. **Doward LC**, McKenna SP, Whalley D, *et al.* The development of the L-QoL: a quality-of-life instrument specific to systemic lupus erythematosus. *Ann Rheum Dis* 2009;**68**:196–200.
3. **Potter C**, Hyrich KL, Tracey A, *et al.* Association of rheumatoid factor and anti-cyclic citrullinated peptide positivity, but not carriage of shared epitope or PTPN22 susceptibility variants, with anti-TNF response in RA. *Ann Rheum Dis* 2009;**68**:69–74.
4. **Smolen JS**, Han C, van der Heijde DM, *et al.*; Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset (ASPIRE) Study Group. Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor blockade. *Ann Rheum Dis* 2009;**68**:823–7.
5. **Buch MH**, Boyle DL, Rosengren S, *et al.* Mode of action of abatacept in rheumatoid arthritis patients having failed tumour necrosis factor blockade: a histological, gene expression and dynamic magnetic resonance imaging pilot study. *Ann Rheum Dis* 2009;**68**:1220–7.
6. **Emery P**, Van Vollenhoven R, Ostergaard M, *et al.* Guidelines for initiation of anti-tumour necrosis factor therapy in rheumatoid arthritis: similarities and differences across Europe. *Ann Rheum Dis* 2009;**68**:456–9.
7. **Bejarano V**, Conaghan PG, Proudman SM, *et al.* Long-term efficacy and toxicity of ciclosporin A in combination with methotrexate in poor prognosis rheumatoid arthritis. *Ann Rheum Dis* 2009;**68**:761–3.
8. **Rudwaleit M**, Landewé R, van der Heijde D, *et al.* The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. *Ann Rheum Dis* 2009;**68**:770–6.
9. **Bennett AN**, Marzo-Ortega H, Emery P, *et al.*; Leeds Spondyloarthropathy Group. Diagnosing axial spondyloarthropathy. The new Assessment in SpondyloArthritis international Society criteria: MRI entering centre stage. *Ann Rheum Dis* 2009;**68**:765–7.
10. **Marzo-Ortega H**, McGonagle D, O'Connor P, *et al.* Baseline and 1-year magnetic resonance imaging of the sacroiliac joint and lumbar spine in very early inflammatory back pain. Relationship between symptoms, HLA-B27 and disease extent and persistence. *Ann Rheum Dis* 2009;**68**:1721–7.
11. **Gilworth G**, Emery P, Gossec L, *et al.* Adaptation and cross-cultural validation of the rheumatoid arthritis work instability scale (RA-WIS). *Ann Rheum Dis* 2009;**68**:1686–90.
12. **Gilworth G**, Emery P, Gossec L, *et al.* Adaptation and cross-cultural validation of the RA-WIS (Work Instability Scale). *Ann Rheum Dis* 2009;**68**:1686–90.
13. **Jarrett SJ**, Sivera F, Cawkwell LS, *et al.* MRI and clinical findings in patients with ankylosing spondylitis eligible for anti-tumour necrosis factor therapy after a short course of etoricoxib. *Ann Rheum Dis* 2009;**68**:1466–9.
14. **Haugeberg G**, Conaghan PG, Quinn M, *et al.* Bone loss in patients with active early rheumatoid arthritis: infliximab and methotrexate compared with methotrexate treatment alone. Exploratory analysis from a 12-month randomised, double-blind, placebo-controlled study. *Ann Rheum Dis* 2009;**68**:1898–901.
15. **Genovese MC**, Breedveld FC, Emery P, *et al.* Safety of biological therapies following rituximab treatment in rheumatoid arthritis patients. *Ann Rheum Dis* 2009;**68**:1894–7.
16. **Kekow J**, Moots RJ, Emery P, *et al.* Patient-reported outcomes improve with etanercept plus methotrexate in active early rheumatoid arthritis and the improvement is strongly associated with remission: the COMET trial. *Ann Rheum Dis* 2010;**69**:222–5.
17. **Furst DE**, Keystone EC, Fleischmann R, *et al.* Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2009. *Ann Rheum Dis* 2010;**69**(Suppl 1):i2–29.
18. **Freeston JE**, Wakefield RJ, Conaghan PG, *et al.* A diagnostic algorithm for persistence of very early inflammatory arthritis: the utility of power Doppler ultrasound when added to conventional assessment tools. *Ann Rheum Dis* 2010;**69**:417–9.
19. **Jones E**, Churchman SM, English A, *et al.* Mesenchymal stem cells in rheumatoid synovium: enumeration and functional assessment in relation to synovial inflammation level. *Ann Rheum Dis* 2010;**69**:450–7.
20. **Alten RE**, Zerbini C, Jeka S, *et al.* Efficacy and safety of pamapimod in patients with active rheumatoid arthritis receiving stable methotrexate therapy. *Ann Rheum Dis* 2010;**69**:364–7.
21. **Machold KP**, Landewé R, Smolen JS, *et al.* The Stop Arthritis Very Early (SAVE) trial, an international multicentre, randomised, double-blind, placebo-controlled trial on glucocorticoids in very early arthritis. *Ann Rheum Dis* 2010;**69**:495–502.
22. **Schoels M**, Knevel R, Aletaha D, *et al.* Evidence for treating rheumatoid arthritis to target: results of a systematic literature search. *Ann Rheum Dis* 2010;**69**:638–43.
23. **Smolen JS**, Aletaha D, Bijlsma JW, *et al.*; T2T Expert Committee. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010;**69**:631–7.
24. **Burr ML**, Naseem H, Hinks A, *et al.*; BIRAC Consortium; YEAR Consortium. PADI4 genotype is not associated with rheumatoid arthritis in a large UK Caucasian population. *Ann Rheum Dis* 2010;**69**:666–70.
25. **Emery P**, Durez P, Dougados M, *et al.* Impact of T-cell costimulation modulation in patients with undifferentiated inflammatory arthritis or very early rheumatoid arthritis: a clinical and imaging study of abatacept (the ADJUST trial). *Ann Rheum Dis* 2010;**69**:510–16.
26. **Bennett AN**, Rehman A, Hensor EM, *et al.* The fatty Romanus lesion: a non-inflammatory spinal MRI lesion specific for axial spondyloarthropathy. *Ann Rheum Dis* 2010;**69**:891–4.
27. **Nam JL**, Winthrop KL, van Vollenhoven RF, *et al.* Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. *Ann Rheum Dis* 2010;**69**:976–86.
28. **Smolen JS**, Landewé R, Breedveld FC, *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2010;**69**:964–75.
29. **Tan RJ**, Gibbons LJ, Potter C, *et al.*; BRAGGSS. Investigation of rheumatoid arthritis susceptibility genes identifies association of AFF3 and CD226 variants with response to anti-tumour necrosis factor treatment. *Ann Rheum Dis* 2010;**69**:1029–35.
30. **Robinson JI**, Barrett JH, Taylor JC, *et al.*; YEAR Consortium; BRAGGSS. Dissection of the FCGR3A association with RA: increased association in men and with autoantibody positive disease. *Ann Rheum Dis* 2010;**69**:1054–7.
31. **Cohen SB**, Keystone E, Genovese MC, *et al.* Continued inhibition of structural damage over 2 years in patients with rheumatoid arthritis treated with rituximab in combination with methotrexate. *Ann Rheum Dis* 2010;**69**:1158–61.
32. **Haugeberg G**, Bennett AN, McGonagle D, *et al.* Bone loss in very early inflammatory back pain in undifferentiated spondyloarthropathy: a 1-year observational study. *Ann Rheum Dis* 2010;**69**:1364–6.
33. **Schoels M**, Aletaha D, Smolen JS, *et al.* Follow-up standards and treatment targets in rheumatoid arthritis: results of a questionnaire at the EULAR 2008. *Ann Rheum Dis* 2010;**69**:575–8.
34. **Eyre S**, Flynn E, Martin P, *et al.* No evidence for association of the KLF12 gene with rheumatoid arthritis in a large UK cohort. *Ann Rheum Dis* 2010;**69**:1407–8.
35. **Eyre S**, Hinks A, Flynn E, *et al.* Confirmation of association of the REL locus with rheumatoid arthritis susceptibility in the UK population. *Ann Rheum Dis* 2010;**69**:1572–3.
36. **Orozco G**, Eyre S, Hinks A, *et al.*; Wellcome Trust Case Control consortium YEAR Consortium. Association of CD40 with rheumatoid arthritis confirmed in a large UK case-control study. *Ann Rheum Dis* 2010;**69**:813–16.
37. **Emery P**, Durez P, Dougados M, *et al.* Impact of T-cell costimulation modulation in patients with undifferentiated inflammatory arthritis or very early rheumatoid arthritis: a clinical and imaging study of abatacept (the ADJUST trial). *Ann Rheum Dis* 2010;**69**:510–16.
38. **Saleem B**, Keen H, Goeb V, *et al.* Patients with RA in remission on TNF blockers: when and in whom can TNF blocker therapy be stopped? *Ann Rheum Dis* 2010;**69**:1636–42.
39. **Barkham N**, Coates LC, Keen H, *et al.* Double-blind placebo-controlled trial of etanercept in the prevention of work disability in ankylosing spondylitis. *Ann Rheum Dis* 2010;**69**:1926–8.
40. **Emery P**, Deodhar A, Rigby WF, *et al.* Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE)). *Ann Rheum Dis* 2010;**69**:1629–35.
41. **Dixon WG**, Hyrich KL, Watson KD, *et al.*; BSRBR Control Centre Consortium; British Society for Rheumatology Biologics Register. Influence of anti-TNF therapy on mortality in patients with rheumatoid arthritis-associated interstitial lung disease: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis* 2010;**69**:1086–91.