Association of *CD40* with rheumatoid arthritis confirmed in a large UK case-control study

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ABSTRACT

Objective A recent meta-analysis of published genome-wide association studies (GWAS) in populations of European descent reported novel associations of markers mapping to the *CD40*, *CCL21* and *CDK6* genes with rheumatoid arthritis (RA) susceptibility while a large-scale, case-control association study in a Japanese population identified association with multiple single nucleotide polymorphisms (SNPs) in the *CD244* gene. The aim of the current study was to validate these potential RA susceptibility markers in a UK population.

Methods A total of 4 SNPs (rs4810485 in *CD40*, rs2812378 in *CCL21*, rs42041 in *CDK6* and rs6682654 in *CD244*) were genotyped in a UK cohort comprising 3962 UK patients with RA and 3531 healthy controls using the Sequenom iPlex platform. Genotype counts in patients and controls were analysed with the χ^2 test using Stata.

Results Association to the *CD40* gene was robustly replicated ($p=2\times10^{-4}$, OR 0.86, 95% CI 0.79 to 0.93) and modest evidence was found for association with the *CCL21* locus ($p=0.04$, OR 1.08, 95% CI 1.01 to 1.16). However, there was no evidence for association of rs42041 (*CDK6*) and rs6682654 (*CD244*) with RA susceptibility in this UK population. Following a meta-analysis including the original data, association to *CD40* was confirmed ($p=7.8\times10^{-8}$, OR 0.87 (95% CI 0.83 to 0.92).

Conclusion In this large UK cohort, strong association of the *CD40* gene with susceptibility to RA was found, and weaker evidence for association with RA in the *CCL21* locus.

INTRODUCTION

Genome-wide association studies (GWAS) have led to a breakthrough in the search for complex disease susceptibility markers.[1] Specifically for rheumatoid arthritis (RA), these studies have detected a number of new susceptibility loci, including the 6q23,[2–4] *TRAF1/C5*,[5–9] *PRKCQ*, *KIF5A* and *IL2RB* genetic regions.[10] Recently, a meta-analysis of the Wellcome Trust Case Control Consortium (WTCCC) GWAS and a US GWAS[4 5] confirmed association to *PRKCQ*, *KIF5A* and *MMEL* and identified additional RA-associated markers mapping to the *CD40*, *CCL21* and *CDK6* loci,[11] that have yet to be confirmed in an independent UK population. In addition, a recent case-control association study in a Japanese population identified two functional variants mapping to the *CD244* gene, rs3766379 and rs6682654, that were associated with RA, again yet to be tested for association in a UK population.[12]

These studies therefore add to the recent explosion in the number of loci reported to be associated with RA susceptibility. In order for these loci to be confirmed as risk factors for RA, well powered validation studies are required to support these initial findings.

The aims of this study were, therefore, first to validate the additional RA markers derived from the recent meta-analysis (*CD40*, *CCL21* and *CDK6*) in an independent UK population and, second, to investigate a functional *CD244* variant reported to be associated with RA in the Japanese study.[11 12]

METHODS

Patients with RA (n=3962) were recruited from six centres (Manchester, Sheffield, Leeds, Aberdeen, Oxford and London) across the UK. All patients were Caucasian of North European ancestry and all fulfilled the 1987 American College of Rheumatology classification criteria modified for genetic studies.[13 14] Clinical and demographic characteristics of the cohort are detailed in supplementary table 1. Briefly, 71.8% participants were women, 72.1% were rheumatoid factor positive and 67.9% carried anti-citrullinated protein antibodies (ACPA) as recognised by the anti-cyclic citrullinated protein (CCP) antibody test. This cohort is therefore representative of a hospital-based series of patients with RA. Autoantibody status data was available for 3723 and 2281 patients for rheumatoid factor (RF) and anti-CCP, respectively. Healthy controls (n=3531) were recruited from five of the six centres (patients only recruited from London). All participants were recruited after providing informed consent and the study was approved by the North West Research Ethics Committee (MREC 99/8/84).

Genotyping was performed using the Sequenom iPlex platform (http://www.sequenom.com) according to the manufacturer's instructions. All genotyping was performed at the arc Epidemiology Unit, Manchester. Only samples and single nucleotide polymorphisms (SNPs) exceeding a 90% success rate were used in the analysis.

Genotype counts in patients and controls were analysed using Stata software (Stata, College Station, Texas, USA) with the χ^2 test. For the meta-analysis, the Breslow–Day test for homogeneity and the Cochran Mantel–Haenszel test were performed using Stata. For all the tests performed, p values <0.0125 were considered statistically significant, after applying Bonferroni correction for four comparisons.

Power calculations were performed using the Quanto V.0.5 software (Department of Preventive Medicine University of Southern California, California, USA), considering minor allele frequencies and ORs similar to those found in previous studies [4 5 11 12] at the 5% significance level.

RESULTS

We selected four polymorphisms previously reported as RA susceptibility markers for testing in the current study:

(1) rs4810485, located in the second intron of the *CD40* gene;
(2) rs2812378, mapping to the 5′ untranslated region of *CCL21*;
(3) rs42041, positioned in a *CDK6* intron[11];
(4) rs6682654, located in *CD244*, which is an almost perfect proxy of the functional RA marker for the Japanese population within this gene, rs3766379 (D′=1, r^2=0.97).[12]

Genotype frequencies conformed to Hardy–Weinberg expectations in patients and controls for all the polymorphisms under study. The estimated power of the study was 86% for rs481048, 77% for rs2812378, 60% for rs42041 and 99% for rs6682654.

Table 1 shows the results of this validation study. Allele frequencies were similar to those previously described in a US population for the *CD40*, *CCL21* and *CDK6* markers.[11] We found that the minor T allele of *CD40* rs4810485 was significantly increased in healthy controls compared to patients with RA (p=2×10^{-4}, OR 0.86, 95% CI 0.79 to 0.93). This is in accordance with the previous study by Raychaudhuri *et al*.

When we analysed *CCL21* rs2812378, we observed a higher frequency of the minor C allele in patients with RA as previously described,[11] although this skewing seemed to have a more modest effect in our population (p=0.04, OR 1.08, 95% CI 1.01 to 1.16). With regard to *CDK6* rs42041, no evidence of association with RA was found in our UK population (table 1).

Additionally, we examined the functional *CD244* variant rs6682654, which was previously shown to be associated with RA in a Japanese population.[12] Linkage disequilibrium (LD) between this SNP and the other marker within *CD244*, rs3766379, also reported to be associated with RA in the Japanese study, is higher in the Caucasian population (r^2=0.97, D′=1) than in the Japanese population (r^2=0.87, D′=1).[15] When we compared the distribution of allele and genotype frequencies of rs6682654 between patients and controls, we did not find statistically significant differences (table 1). Allele frequencies of the reference G allele were lower in the UK population than in the previously described Japanese population (0.43 and 0.44 in patients and controls, respectively, for the UK population vs 0.66 and 0.59 in patients and controls, respectively, for the Japanese population), which is in accordance with the data deposited in HapMap (http://www.hapmap.org).

Stratification analysis of the four polymorphisms under study showed that the rs4810485 *CD40* SNP was strongly associated with the presence of RF and anti-CCP antibodies (p=8.10×10^{-6}, OR 0.82, 95% CI 0.75 to 0.89 and p=9.52×10^{-5}, OR 0.81, 95% CI 0.73 to 0.90, respectively). *CCL21* rs2812378 also showed this trend, but p values for the association with seropositive disease were modest (p=0.02, OR 1.10, 95% CI 1.01 to 1.18 and p=0.03, OR 1.10, 95% CI 1.01 to 1.21, for RF and anti-CCP RA, respectively) (supplementary table 2).

Meta-analysis of these markers was undertaken, pooling data from the previously published RA GWASs,[4 5 11] together with data from a validation cohort from the US[11] and our validation study in a UK cohort. p Values for the Breslow–Day test were 0.31 for rs4810485, 0.81 for rs2812378 and 0.02 for rs42041 (table 2). The meta-analysis revealed strong evidence of association with the *CD40* variant and a more modest, but suggestive association with the *CCL21* variant. The evidence for association with *CDK6* was relatively weak.

The rs6682654 SNP mapping to *CD244* and showing evidence for association with RA in a Japanese population[12] was not tested in the meta-analysis by Raychaudhri *et al*.[11] In order to investigate whether a weak effect on susceptibility could be detected in a UK population, we performed a meta-analysis of the variant, combining imputed data from the WTCCC dataset with that derived from direct genotyping in the current validation study. Pooled analysis revealed no association with RA in the UK population (p=0.87, OR 1.004, 95% CI 0.95 to 1.06). Joint analysis of the Japanese and UK cohorts was not feasible, due to the high degree of genetic heterogeneity between the populations ($p_{Breslow–Day}$=1.8×10^{-6}).

DISCUSSION

In this large UK cohort, we have found strong association of the rs4810485 *CD40* variant with susceptibility to RA, and weaker evidence for association with RA in the *CCL21* locus. We found no evidence for association with either the *CDK6* locus or the

Table 1 Validation study of novel rheumatoid arthritis (RA) susceptibility markers in a UK population

Locus	SNP	Minor/major allele	MAF RA	MAF controls	Genotype frequency, no (%) RA 11	RA 12	RA 22	Controls 11	Controls 12	Controls 22	p For allele	OR (95% CI) for allele	p For genotypes	p For 12+22 vs 11
CD40	rs4810485	T/G	0.23	0.25	165 (4.5)	1334 (36.2)	2184 (59.3)	173 (5.7)	1189 (39.1)	1681 (55.2)	2×10^{-4}	0.86 (0.79 to 0.93)	0.001	0.02
CCL21	rs2812378	G/A	0.37	0.35	478 (12.9)	1752 (47.2)	1478 (39.9)	377 (12.5)	1339 (44.5)	1294 (43)	0.04	1.08 (1.01 to 1.16)	0.03	0.65
CDK6	rs42041	G/C	0.25	0.25	228 (6.1)	1402 (37.8)	2079 (56.1)	182 (6.1)	1125 (38)	1655 (55.9)	0.91	0.99 (0.92 to 1.08)	0.99	0.99
CD244	rs6682654	G/A	0.43	0.44	638 (18.1)	1756 (49.8)	1132 (32.1)	571 (19.9)	1394 (48.5)	909 (31.6)	0.20	0.96 (0.89 to 1.02)	0.19	0.07

MAF, minor allele frequency; SNP, single nucleotide polymorphism.

Table 2 Meta-analysis of newly identified rheumatoid arthritis (RA) markers in populations of European ancestry

Locus	SNP	GWAS meta-analysis[11] p Value	GWAS meta-analysis[11] OR	US validation[11] p Value	US validation[11] OR	UK validation p Value	UK validation OR (95% CI)	Meta-analysis p Value	Meta-analysis OR (95% CI)	Breslow–Day p value
CD40	rs4810485	2.4×10^{-7}	0.83	0.003	0.91	2×10^{-4}	0.86 (0.79 to 0.93)	7.8×10^{-8}	0.87 (0.83 to 0.92)	0.31
CCL21	rs2812378	6.9×10^{-5}	1.13	9.7×10^{-4}	1.10	0.04	1.08 (1.01 to 1.16)	1.2×10^{-4}	1.09 (1.04 to 1.14)	0.81
CDK6	rs42041	5.5×10^{-5}	1.15	0.01	1.08	0.91	0.99 (0.92 to 1.08)	0.002	1.08 (1.03 to 1.14)	0.02

GWAS, genome-wide association studies; SNP, single nucleotide polymorphism.

CD244 variant, previously reported to be associated with RA in Caucasian and Japanese populations, respectively.

The *CD40* and *CCL21* genes both encode proteins that are involved in immune regulation. CD40 is expressed in a wide variety of immune cells, including B cells, monocytes and dendritic cells, while its ligand, CD154, is expressed by activated CD4 T cells. Binding of CD154 to CD40 provides a critical stimulus for B cell proliferation, immunoglobulin production, isotype switching and upregulation of other costimulatory molecules including B7-related molecules.[16] CD40–CD154 interaction appears to have an important role in RA, as expression of CD154 on CD4 T cells in RA promotes increased activation of CD4 T lymphocytes and is associated with active disease. Indeed, blockade of this pathway has been suggested as a potentially useful therapeutic approach in RA and in autoimmune disease in general.[16 17] It is interesting to note that the *CD40* marker was strongly associated with anti-CCP and RF-positive RA, which suggest that this polymorphism, or other/s in LD with it, could play a role in the regulation of B cell response and the production of autoantibodies. The *CCL21* gene encodes a protein that is a homeostatic lymphoid chemokine instrumental in the recruitment and organisation of T cells and dendritic cells into secondary lymphoid organs, which participate in lymphoid tissue microanatomical organisation in RA.[18] Both genes, therefore, are plausible candidates in conferring risk of RA. Although we found statistically significant evidence for association with the *CCL21* locus, this would not have remained significant if a correction for multiple testing had been applied and, therefore, confirmation of this locus as an RA susceptibility region will require further investigation in other large data series.

It is becoming well established that there exists an ethnic heterogeneity of genetic susceptibility factors in RA, meaning that findings from one ethnic group may not be readily applicable to all. For example, rs2476601 in the *PTPN22* gene, which is the most robustly validated RA marker in European populations after human leukocyte antigen (HLA), is not polymorphic in Asian populations.[19] In contrast, polymorphisms in *PADI4* are far more strongly associated with RA in Far East populations than European populations, despite having a comparable allele frequencies.[19–21] Other RA susceptibility loci, such as *STAT4*, are common to European and Asian populations.[9 22–24] More relevant to the current study, it has recently been reported that the *CD40* and *CCL21* variants tested in the present study, are not associated with RA in a Korean population.[25] However, it is possible that the *CD244* SNP tested in the current study is in LD with the true causative variant in the Japanese population, but not in the UK population, which could explain the lack of replication of the association of this marker.

This is the first study to test the association of *CD244* with RA in a European population, but we have found no evidence for association, despite it being a functional polymorphism with a regulatory effect on the transcription of *CD244*.[12] Insufficient power is an unlikely cause of the lack of replication, since we achieved >98% power to detect an association with an effect size similar to that reported in the prior Japanese study[12] at a 5% significance level. However, the 'winner's curse' means that effect sizes are often overestimated in the first study in which they are reported. It is possible that the effect size at this locus is smaller and that, by chance, it has not been detected in the current study. The lack of power of individual studies may be overcome by meta-analysis where published data is available and this is particularly pertinent to the *CDK6* rs42041 SNP where the power to detect association in the sample set tested in the current study was low (approximately 60%). The meta-analysis presented here yielded a statistically significant, yet modest, association (p=0.002, OR 1.08, 95% CI 1.03 to 1.14) of the *CDK6* rs42041 marker with RA susceptibility. It should be noted that we detected some heterogeneity in the effect sizes between studies ($p_{Breslow–Day}$=0.02), so the pooled OR should be considered with caution and further validation in independent cohorts will be required in order to clarify the role of this variant in RA susceptibility. For the *CD244* marker, by contrast, no evidence for association was detected even after pooled analysis of the UK WTCCC and validation datasets, which included approximately 5400 patients with RA and approximately 5800 healthy controls. In this case, genetic heterogeneity would appear to explain the lack of replication as allele frequencies for the rs6682654 SNP are significantly different between the Japanese and UK populations.

In the past year, the first wave of GWAS has improved our understanding of the genetic basis of common, complex diseases, including RA. These studies have made possible the identification of new RA susceptibility loci, such as those mapping to the 6q23, *TRAF1/C5*, *PRKCQ*, *KIF5A*, *STAT4* and now *CD40*. However, these initial GWAS have shown that the effect sizes resulting from associations with common SNPs are modest and, therefore, the remaining RA susceptibility genes may have even smaller effect sizes. Validation studies using large sample sizes and ethnically different populations as well as meta-analysis will be essential to robustly define new potential susceptibility loci. Only then will the investment in fine mapping and functional studies be justified to identify the aetiological variants within the validated loci. In conclusion, we have validated association of *CD40* rs4810485 and detected weak evidence for association of *CCL21* rs2812378 with RA in a UK population, laying the foundations for further studies of the functional and genetic effects of these variants in conferring risk of 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 99/8/84).

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For more information on the WTCCC and YEAR Consortiums, see supplementary material.

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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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