Ten single-nucleotide polymorphisms (SNPs) were selected for genotyping. These included the tagging SNP (rs1248696) marking the haplotype over-represented in Crohn's disease and an additional nine SNPs selected to provide 100% gene coverage across the *DLG5* gene using the available HapMap Phase1 data ($r^2 > 0.8$ and minor allele frequencies $> 5\%$; <http://www.broad.mit.edu/mpg/tagger/>; table 1).⁷ The sample size was calculated to ensure that the study had 80% power to detect the same effect size of 1.62 reported in the original inflammatory bowel disease study at the 5% significance level. Allele and genotype frequencies were compared between patients with PsA ($n = 356$) and population controls ($n = 356$). All were Caucasians, and PsA was defined as the presence of both psoriasis and inflammatory arthritis regardless of the rheumatoid factor status. Both the case and control cohorts have been described previously.⁶ Genotyping was performed using the Sequenom MassArray platform (Sequenom, San Diego, California, USA). This study was approved by the North West Multicentre Research Ethics Committee (MREC 99/8/84), and all subjects provided informed consent.

Genotype frequencies for both PsA cases and controls conformed to Hardy-Weinberg expectations and allele frequencies were similar to those reported previously in European populations where data were available. Genotype frequencies between PsA cases and controls were not significantly different for any of the SNPs tested (table 1). Stratifying by the presence or absence of rheumatoid factor, by sex or by performing subset analysis on those with type 1 psoriasis did not show evidence of an association in subgroups of patients (data not shown). Strong linkage disequilibrium existed across the gene ($D' > 0.9$). Haplotype analysis showed no difference in haplotype distributions between cases and controls (data not shown).

The association of the *DLG5* gene with Crohn's disease has been replicated, but not in all populations and not always with the same SNP found in the original study.⁸ To ensure that an effect with another variant was not missed in this study,

comprehensive genotyping across the gene and haplotype analysis was undertaken, but no association with PsA was found. We conclude that the *DLG5* gene does not seem to be a major susceptibility gene for PsA in the UK population.

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MHC2TA is associated with rheumatoid arthritis in Japanese patients

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Many diseases have increased expression of both major histocompatibility complex (MHC) class I and II molecules, and in particular the class II genes in the human leucocyte antigen region in particular are known to influence many chronic inflammatory diseases. Recently, a -168A→G polymorphism (rs3087456) in the type III promoter of MHC2TA, which has a pivotal role in MHC class II regulation, was found to be associated with increased susceptibility to rheumatoid arthritis in a Swedish population.¹ However, most replication studies in other populations did not reproduce this finding, except a Spanish study.²⁻⁶ The purpose of this study was to see if the reported association could be observed in a Japanese population.

DNA samples were obtained from 1128 Japanese patients with rheumatoid arthritis and 455 sex-matched controls as detailed in the previous study.⁷ Genotypes of rs3087456 were

determined by the TaqMan method as described elsewhere.⁷ The association between susceptibility to rheumatoid arthritis and rs3087456 was estimated by the χ^2 test implemented in R software package (<http://www.r-project.org/>).

We found a significant association between susceptibility to rheumatoid arthritis and the MHC2TA polymorphism ($p = 0.003$, odds ratio (OR) 1.37, table 1). Although the previously reported association was clearly replicated, the frequency of the risk allele was significantly different in the Japanese population compared with that reported in the Swedish population; it was a major allele in the Japanese population, whereas it was a minor allele in the Swedish population.

Ethnic differences can well account for the difference in allelic frequencies observed in our results compared with those of the Swedish study. It is not uncommon to see pronounced

Table 1 Distribution of *MHC2TA* -168A→G in patients with rheumatoid arthritis and controls*

	AA (%)	AG (%)	GG (%)	G allele frequency	p Value	OR (95% CI)
RA (n = 1121)	31 (2.8)	253 (22.6)	837 (74.2)	0.86	0.003	1.37
Controls (n = 450)	15 (3.3)	135 (30)	300 (66.7)	0.82		(1.11 to 1.7)

RA, rheumatoid arthritis.

*The distribution of the genotypes followed the Hardy–Weinberg equilibrium for both groups.

differences in allele frequency between ethnic groups.^{8–9} Interestingly, despite the significant differences in observed allelic frequency, the prevalence of rheumatoid arthritis in Japanese and Swedish patients were similar, 0.3–0.5% and 0.5%, respectively.^{10–11} This might indicate that the genetic contribution of *MHC2TA* to rheumatoid arthritis is relatively low, further suggested by the low OR.

The reason for the discrepancy observed in the association studies is difficult to explain. Although the simplest explanation for the discrepancy may be that the *MHC2TA* has a more important role for disease susceptibility in Japanese, Spanish and Swedish patients than in other populations, this is not an intelligible explanation on the basis of genetic distances among these ethnic populations.

Negative association studies often lack sufficient power to detect genetic effects. Indeed, the studies with negative association had insufficient power to detect an OR of 1.29, as observed in the Swedish study (power of <80%, $p = 0.05$, 21% frequency of risk allele. This low power may be a limitation of the studies.

Exploration of gene–environmental interaction might help to understand the discrepancy underlying the association studies. Differences in lifestyle might exist in varying degrees among these populations. Further larger detailed cohort studies in each population are necessary to detect the interaction effects on the susceptibility to rheumatoid arthritis.

We conclude that *MHC2TA* is strongly associated with rheumatoid arthritis in a Japanese population. Replication across ethnicity provides strong evidence that *MHC2TA* may be associated with susceptibility to rheumatoid arthritis. Further studies in other ethnic groups are necessary to draw definite conclusions.

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