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ERAP2 is associated with ankylosing spondylitis in *HLA-B27*-positive and *HLA-B27*-negative patients

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The association of endoplasmic reticulum aminopeptidase 2 (*ERAP2*) with ankylosing spondylitis (AS) was recently described in the large International Genetics of AS Consortium Immunochip study.[1] Variants in *ERAP2* have also been associated with inflammatory bowel disease, psoriasis, acute anterior uveitis and birdshot chorioretinopathy.[2–5] Subsequent investigation demonstrated an association of *ERAP2* with AS which was present when one conditioned on one of the two independent haplotypes of *ERAP1* associated with AS or when *HLA-B27*-negative patients were analysed separately.[1] These two analyses provide analogous evidence for the association of *ERAP2* with AS in *HLA-B27*-negative cases because of the genetic interaction between *HLA-B27* and the AS-associated *ERAP1* variants in AS cases. *ERAP1* and *ERAP2* are located on chromosome 5q15 in the opposite orientation. The locus is challenging to analyse because of the strong linkage disequilibrium (LD) across the locus and the epistasis between *ERAP1* and *HLA-B* alleles associated with AS. We therefore sought to investigate the association of *ERAP2* with AS in *HLA-B27*-positive patients.[6] This is of clinical importance because functional studies have demonstrated that the strongly AS-protective variant rs2248374 causes a functional ERAP2 protein knockout, because its G allele causes a loss of ERAP2 protein expression.[57] There is also a variant of *ERAP2* which changes its enzyme catalytic activity and specificity (rs2549782, K392A[8]). Because this is in almost complete LD with rs2248374 (1000 Genomes D′=1.00, r^2=0.90), it is almost never translated in vivo. Further, the very strong LD between these markers means that analysis of rs2549782 for association would yield results almost identical to the results for rs2248374 presented below. Therefore, it is of relevance to determine whether the association of *ERAP2* with *HLA-B27*-negative disease is also found in *HLA-B27*-positive cases, since ERAP inhibition may offer a novel therapeutic for AS.[9]

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Data sharing statement The data that the study uses have been fully detailed elsewhere.[1]

We studied European Immunochip *HLA-B27*-positive patients (n=7772), *HLA-B*27*-positive controls (n=1204) and unselected European controls (n=13,578). *HLA-B*27*-positive status was taken as an imputed allele dosage of 0.6 or greater in the *HLA-B*27* tag SNP rs116488202 that has 99% sensitivity and 99% specificity for *HLA-B*27* in Europeans.[1] We used rs2248374 as a marker of the associated *ERAP2* haplotype.

We then constructed a range of logistic regression models that controlled for *ERAP1* haplotype association and included *HLA-B27* controls and unselected controls and also included the first four eigenvectors to control for any potential population stratification. Analyses including only *HLA-B27*-positive controls are somewhat underpowered relative to the unselected control cohort but were included for illustrative purposes. Analyses were performed using R and the glm() function.

The results show that when using only *HLA-B*27*-positive patients with AS and either *HLA-B*27*-positive or unselected controls there is significant association at the *ERAP2* locus (6.03×10^{-4} and 3.54×10^{-9} respectively; table 1 and figure 1). We also present the models excluding the two associated *ERAP1* haplotypes to demonstrate that the nearby influence of these associations masks the underlying *ERAP2* association.

The significance of this finding is substantial. First, the conditional association noted in all patients with AS previously could have been solely the result of association in *HLA-B*27*-negative patients in the dataset.[1] These data demonstrate that excluding *HLA-B*27*-negative patients still results in a robust level of association in logistic regression models that include only *HLA-B*27*-positive patients. The finding that *ERAP2* is associated with protection from AS can now be unequivocally extended from *HLA-B*27*-negative patients with AS to all patients with AS, meaning potentially 8–9 times more patients could benefit from ERAP2 inhibition. Such aminopeptidase inhibitors are currently in development[10] and have exciting therapeutic potential for AS and other immune-mediated diseases including inflammatory bowel disease, uveitis and psoriasis.

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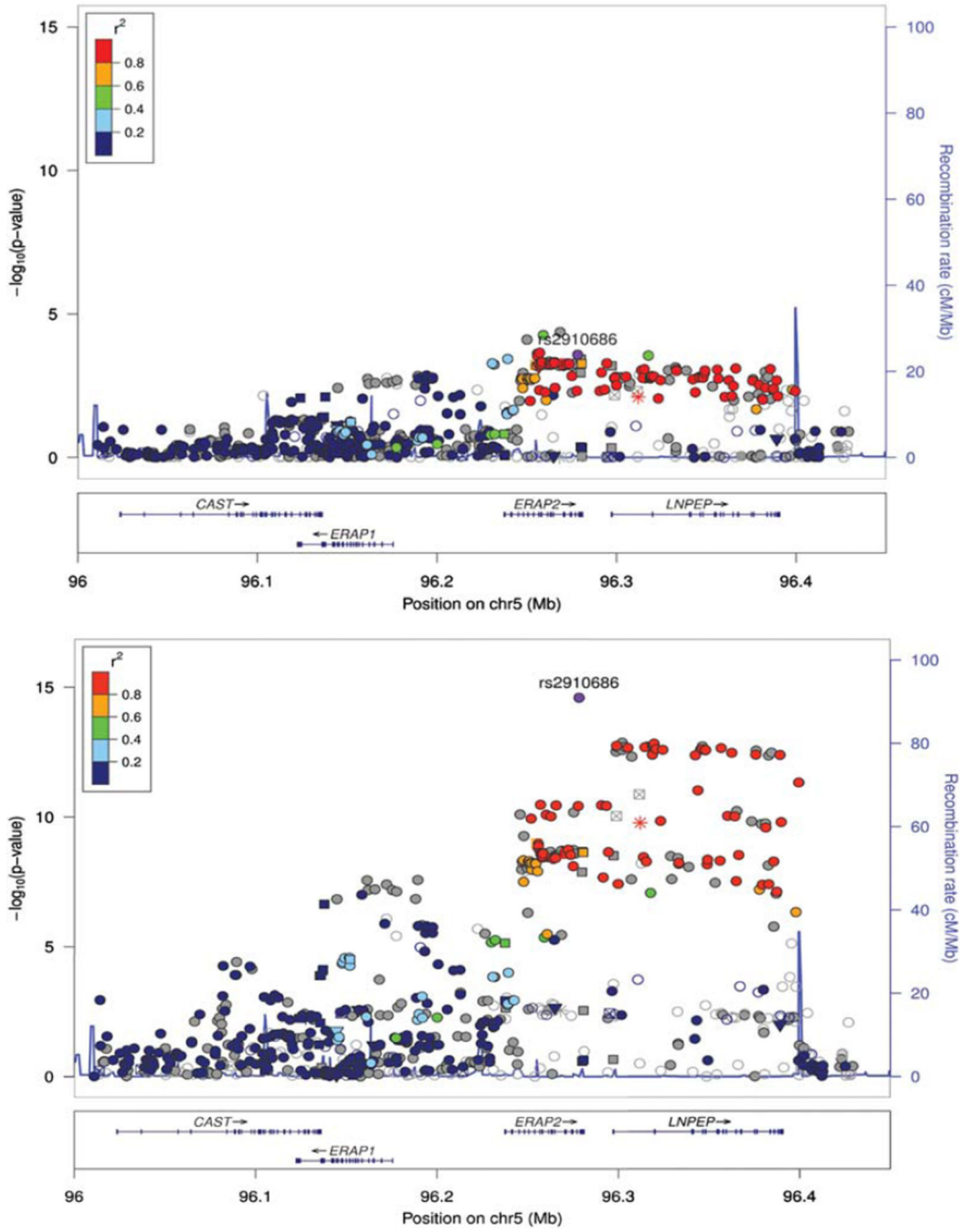

Figure 1.

Local association plots of the *ERAP2* locus when the association model using *HLA-B27*-positive controls (upper) and unselected controls (lower) are used in logistic regression models that incorporate the two independent ankylosing spondylitis-associated *ERAP1* haplotypes, rs30187 and rs10050860, as covariates.

Table 1

Logistic regression models of *ERAP2* (rs2248374) association controlling for the AS-associated *ERAP1* haplotypes (tagged by rs30187 and rs10050860) in HLA-B27-positive cases and either HLA-B27-positive or unselected controls

Model	Controls	rs2248374 G allele β	SE	OR (95% CI)	p Value
rs2248374+rs30187+rs10050860+1st 4 eigenvectors	HLA-B27 positive	−0.16	0.047	0.85 (0.78 to 0.93)	6.03×10^{-4}
rs2248374+rs30187+rs10050860+1st 4 eigenvectors	Unselected	−0.13	0.021	0.88 (0.85 to 0.92)	3.54×10^{-9}
rs2248374+1st 4 eigenvectors	HLA-B27 positive	−0.041	0.044	0.96 (0.88 to 1.05)	0.36
rs2248374+1st 4 eigenvectors	Unselected	−0.028	0.020	0.97 (0.93 to 1.01)	0.16

AS, ankylosing spondylitis.