A common functional variant of endoplasmic reticulum aminopeptidase 2 (ERAP2) that reduces major histocompatibility complex class I expression is not associated with ankylosing spondylitis

Sr, The strong genetic association between AS and HLA-B27 has defied explanation for nearly 40 years. However, the additional discovery of a strong association between AS and ERAP1 (endoplasmic reticulum aminopeptidase 1), a gene that almost certainly operates in the trimming of peptides for optimal binding to MHC class I molecules, has rekindled hopes of rapid advances in this field [1]. It has been suggested that another aminopeptidase, endoplasmic reticulum aminopeptidase 2 (ERAP2), may act in concert with ERAP1, trimming residues inefficiently removed by ERAP1 [2]. The association described recently between ERAP2 and Crohn’s disease, which shares many clinical and genetic overlaps with AS [3], suggests that ERAP2 is worthy of further study in AS. An experiment of nature allows us to do this relatively simply.

ERAP2 has evolved under balancing selection, similar to the MHC, and includes a high-frequency variant (~50%) that influences antigen presentation [4]. A single nucleotide polymorphism (SNP), rs2248374 (A to G), located within the 5’ canonical splice site of exon 10, results in an alternatively spliced ERAP2 mRNA that is degraded by nonsense-mediated decay (NMD). Homozygosity for the minor G allele (carried by ~25% of the population) results in failure to express ERAP2 protein; in turn this genotype may act in concert with ERAP1, trimming residues inefficiently removed by ERAP1 [2]. The association described recently between ERAP2 and Crohn’s disease, which shares many clinical and genetic overlaps with AS [3], suggests that ERAP2 is worthy of further study in AS. An experiment of nature allows us to do this relatively simply.

**Table 1** Genotypes, minor allele frequency (MAF), OR, 95% CI and P-value for the ERAP2 SNP rs2248374

| Patients and controls | Genotype counts | MAF | OR (95% CI) | P-value |
|-----------------------|-----------------|-----|-------------|--------|
| AS cases (n = 470)    | AA 125, AG 245, GG 100 | 0.47 | 1.07 (0.77, 1.14) | 0.46 |
| Controls (n = 420)    | AA 128, AG 201, GG 91 | 0.46 |             |        |
be achievable. Our study was insufficiently powered to do this.

**Rheumatology key message**

- Despite its major functional effect on ERAP2 expression, rs2248374 shows no association with AS.

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**Relapsing polychondritis-associated meningitis and encephalitis: response to infliximab**

Sir, Relapsing polychondritis (RPC) is an uncommon systemic inflammatory disorder of unknown origin. A minority of patients with RPC develop neurological involvement (3%) [1]. The prognostics of patients with RPC complicated by meningoencephalitis (ME) is poor. The reported mortality of RPC-associated meningitis is 12% (3 out of 25 patients), and that of patients with RPC-associated encephalitis is 36.4% (4 out of 11 patients) [2–8]. Therapy with infliximab has been effective in several cases of resistant RPC. Nevertheless, the effects of anti-TNF-α therapy on RPC-associated meningitis and encephalitis have not previously been described. We report a patient with RPC and recurrent episodes of ME refractory to therapy with high-dose glucocorticoids and CYC, who had a satisfactory and long-lasting response to therapy with infliximab.

A 57-year-old male who immigrated 8 years ago from Ecuador presented with fever (up to 39°C), severe headache and two generalized seizures. During the previous 4 years, he had had one episode of erythema nodosum, and several episodes of symmetrical polyarthritis (hands and wrists), auricular chondritis, painful red eyes and dizziness, with the diagnoses of scleritis, cochlear dysfunction and neural deafness.

On admission, he was febrile (38.5°C) and confused with positive meningeal signs and a normal CT scan of the brain. Lumbar puncture (LP) disclosed 700 cells/ml, 98% lymphocytes, glucose 50 mg/dl and proteins 75 mg/dl. Cerebrospinal fluid (CSF) studies were negative for bacteria, virus, fungi and parasites or abnormal cells. Peripheral blood leucocytosis (20 × 10^9/l), 90% neutrophils and elevated acute-phase reactant proteins were observed. Kidney and liver function, ANAs, ANCAs, RF, urinalysis and serological tests for HIV, hepatitis B virus, hepatitis C virus, CMV, EBV, treponema, rickettsias, borrelia, coxieila, brucella and echinococcus were all normal or negative. MRI of the brain showed small T2 gadolinium-enhanced lesions in the periventricular white matter of both cerebral hemispheres (Fig. 1b). The patient improved with high-dose i.v. methylprednisolone and was discharged.

During the following 20 months, he had seven admissions for ME with negative CSF studies. These episodes occurred while the patient was not taking any medications previously associated with ME, including non-steroidal anti-inflammatory agents. Although these episodes of ME improved with high-dose i.v. glucocorticoids plus...