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SPONDYLOARTHROPATHIES

HLA-B27 and ERAP1 contribute to ankylosing spondylitis via aberrant peptide processing and presentation

Ankylosing spondylitis (AS) is a highly heritable spondyloarthropathy that has been shown to be strongly associated with HLA-B27 variants, in addition to a number of other genetic loci, including *IL23R*, *ERAP1*, *KIF21B*, and the intergenic regions 2p15 and 21q22. A large, collaborative, genome-wide association study recently published in *Nature Genetics* has identified additional loci with strong associations with AS, and also provides insight into the mechanism by which HLA-B27 contributes to disease susceptibility and development.

The genome-wide association study included a total of 3,023 patients of European ancestry who met the modified New York classification criteria for AS and 8,779 controls from the Wellcome Trust Case Control Consortium 2 and the Australo-Anglo-American Spondyloarthritis Consortium. The findings from this 'discovery' cohort were tested in a replication study, comprising an independent population of 2,111 cases and 4,483 controls from the UK, Australia and Canada. In addition to the AS-associated loci that were previously established, the combined analyses identified strong associations with single-nucleotide polymorphisms (SNPs) in or near *RUNX3*, *LTBR-TNFRSF1A*, *IL12B*, *PTGER4*, *TBKBP1*, *ANTXR2* and *CARD9*.

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Gene–gene interaction studies revealed strong evidence of interaction between *HLAB27* and *ERAP1*. *ERAP1* SNPs were associated with AS only in HLA-B27-positive individuals. Although the association between AS and HLA-B27 has been known for several decades, the underlying mechanism of how HLA-B27 contributes to disease has remained unclear. ERAP1 functional studies showed that it acts as a 'peptide trimmer' in the endoplasmic reticulum, reducing the size of peptides that have been partially processed by the proteasome to 9 amino acids, the optimal length for binding and presentation to lymphocytes by HLA class I. Protective allelic variants of ERAP1 displayed decreased rates of substrate trimming (~40% slower), suggesting that inhibition of ERAP1 might be effective in HLA-B27-positive patients with AS.

The authors conclude that, in addition to identifying a number of new genetic loci associated with AS, their findings support the view that HLA-B27 induces AS via a mechanism involving aberrant peptide handling and presentation.

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Original article Evans, D. M. *et al.* Interaction between ERAP1 and HLA-B27 in ankylosing spondylitis implicates peptide handling in the mechanism for HLA-B27 in disease susceptibility. *Nat. Genet.* doi:10.1038/ng.873