SPONDYLOARTHROPATHIES

The devil is in the details—teasing out PsA genetics

A new fine-mapping study of previously reported immune-related susceptibility loci for psoriasis and psoriatic arthritis (PsA) reveals fundamental genetic differences between the two conditions, suggesting the existence of PsA-specific risk factors. “Our findings raise the possibility of treatments to prevent the development of PsA in at-risk individuals in the future, or to identify targets for drug development that may be more effective in PsA,” comment Anne Barton and John Bowes, lead researchers on this study at the University of Manchester, UK.

Although both diseases have a strong genetic component, the heritability of PsA is much greater than that of psoriasis. Previous genotyping studies were, however, unable to distinguish between associations with PsA and those with psoriasis itself.

In the current study, Bowes *et al.* genotyped 1,962 patients with PsA and 8,923 controls with psoriasis. The researchers identified a novel

“Fine mapping ... reveals ... the existence of PsA-specific risk factors”

susceptibility locus for psoriasis in *DENND1B*, a gene of unknown function that is upregulated in T cells. Variants in this gene have previously been linked to risk of inflammatory bowel disease (IBD), primary biliary cirrhosis (PBC) and asthma. Intriguingly, the psoriasis risk variant is highly correlated with the IBD and PBC risk variants, but is independent of the asthma variant.

A novel PsA-specific risk locus at chromosome 5q31 (which also includes a known psoriasis risk locus in *IL13*) is probably involved in regulation of the *SLC22A5* gene (encoding a transmembrane ion transporter implicated in the control of intestinal absorption), which is also linked to IBD—offering the tantalizing suggestion that PsA might be

triggered by gut organisms in genetically susceptible individuals.

The researchers also found distinct PsA risk variants within the *IL23R* psoriasis risk locus, as well as evidence that PsA risk markers co-localize with epigenetic markers of active transcription in CD8⁺ T cells, confirming empirical evidence suggesting a key role for these cells in the pathogenesis of PsA. The team is now conducting functional studies to clarify the mechanisms underpinning these associations. Finally, the researchers identified and validated MHC class I variants linked to PsA: *HLA-C*0602*, an amino acid at position 67 of *HLA-B*, and *HLA-A*0201*—the latter shared with ankylosing spondylitis.

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Original article Bowes, J. *et al.* Dense genotyping of immune-related susceptibility loci reveals new insights into the genetics of psoriatic arthritis. *Nat. Commun.* doi:10.1038/ncomms7046