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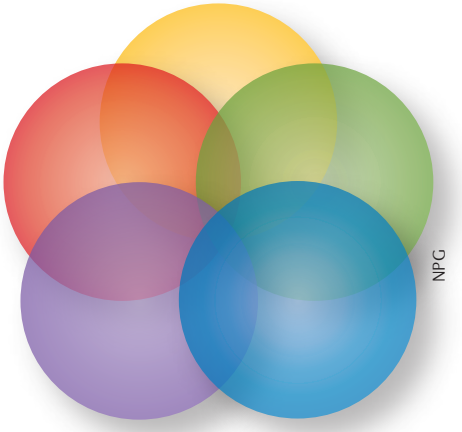

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GENETICS

Novel insights from large cross-disease study

> "they identified … 244 independent association signals, 187 of which were shared by two or more diseases"

The largest cross-phenotype genetic study of autoimmune diseases to date has identified novel disease-associated genetic loci and provided new insights into the clinical relevance of genetic overlap between five seronegative chronic inflammatory conditions.

Ellinghaus *et al.* analysed high-density genotyping data from individuals of European ancestry with no immune-related disease ($n = 34{,}213$), ankylosing spondylitis ($n = 8{,}726$), Crohn disease ($n = 19{,}085$), psoriasis (n = 6,530), primary sclerosing cholangitis ($n = 3{,}408$) or ulcerative colitis ($n = 14{,}413$). Excluding the MHC locus, they identified 169 disease-associated loci that reached genome-wide significance ($P < 5 \times 10^{-8}$); these loci contained 244 independent association signals, 187 of which were shared by two or more diseases. Notably, three of these shared signals had not previously been associated with any of the studied diseases. Although there was substantial genetic overlap between diseases, the analyses also revealed distinct disease-specific genetic architectures (consistent with previous studies) and identified 27 novel disease associations, including 17 for ankylosing spondylitis.

The authors found a significant degree of comorbidity among the five diseases in two independent cohorts and went on to investigate the relevance of genetic sharing to comorbid disease, with a view to identifying whether the observed comorbidity reflected biological pleiotropy or heterogeneity. In the setting of pleiotropy, a single genetic variant has multiple phenotypic effects; that is, one risk variant is associated with two distinct diseases such that an individual carrying the shared risk variant is more likely to acquire both diseases. By contrast, heterogeneity refers to the setting in which a subgroup of disease cases has a higher load of risk variants for the cormorbid disease.

Using an established statistical method that can distinguish between pleiotropy and heterogeneity, the authors showed that the observed comorbidities among the five diseases were best explained by biological pleiotropy. This suggests that patients with comorbid disease are genetically distinct from those without, and that comorbid disease arises from common pathophysiological pathways driven by shared genetic architectures.

Further work is needed to determine whether such pleiotropy occurs in other immune-mediated diseases and also to elucidate the disease-relevant molecular mechanisms that underpin these pleiotropic effects. The authors suggest that future cross-disease genetic studies — using larger cohorts and more detailed, longitudinal clinical data — could inform the development of a new disease classification system based on genetic profiles in addition to traditional diagnostic criteria.

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ORIGINAL ARTICLE Ellinghaus, D. *et al.* Analysis of five chronic inflammatory diseases identifies 27 new associations and highlights disease-specific patterns at shared loci. *Nat. Genet.* http://dx.doi.org/10.1038/ng.3528 (2016)