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GENETICS

Meta-analysis reveals novel overlap in genetic aetiologies of paediatric autoimmune disorders

Genome-wide association studies (GWAS) have identified numerous genetic risk factors for autoimmune diseases, including many that are associated with more than one disease. A meta-analysis of GWAS data now published in *Nature Medicine* highlights that substantial genetic overlap exists across 10 distinct paediatric autoimmune diseases, revealing gene networks and pathways that could be targeted therapeutically.

The total cohort of the case–control study comprised more than 6,035 patients with childhood-onset autoimmune disease—Crohn disease, juvenile idiopathic arthritis (JIA), type 1 diabetes mellitus, ulcerative colitis, common variable immunodeficiency (CVID), systemic lupus erythematosus (SLE), psoriasis, ankylosing spondylitis (AS) and thyroiditis—as well as 10,718 population-based controls with no history of autoimmune or immune-mediated disorders. "We used several genetic association tests to capture genome-wide significant loci across the 10 paediatric autoimmune diseases," explains the study's corresponding author, Hakon Hakonarson of The Children's Hospital of Philadelphia.

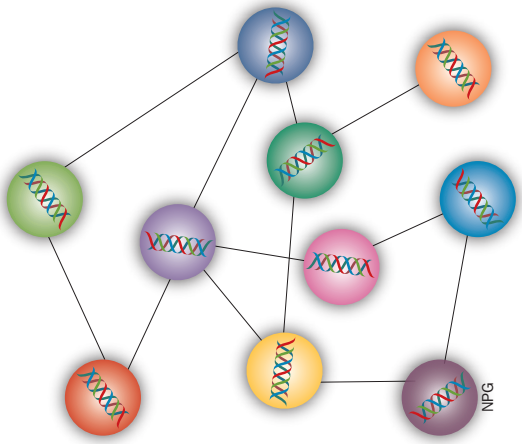
The analysis identified 27 disease-associated loci with at least one single-nucleotide polymorphism (SNP) that reached a conventionally defined genome-wide significance threshold ($P>5\times10^{-8}$). Of the 27 loci with genome-wide significance, 22 (81%) were shared by two or more diseases, and 19 (70%) were shared by three or more diseases. In several instances, a SNP associated with increased risk of one disease had a protective effect in another disease. Although most of the 27 loci mapped to previously known autoimmune genes, five (*CD40LG*, *ADGRL2*, *TENM3*, *ANKRD30* and *ADCY7*) had not been previously reported at levels of genome-wide significance in autoimmune diseases.

The functional and biological relevance of the SNP associations was supported by experimental and predictive data from the public domain. The disease-associated SNPs were enriched for DNase-hypersensitivity sites, expression quantitative trait loci, transcription-factor binding sites and microRNA binding sites. "The study reinforces the idea that associated variants are outside traditional gene-coding regions and are enriched for marks for regulatory activity," comments Stephen Eyre of Manchester University, who was not involved in the study.

The international team of researchers also found that transcript levels of the disease-associated genes were higher in immune cells and/or tissue types than in non-immune types (by contrast, no such immune-specific enrichment was seen with schizophrenia-associated genes). Moreover, the disease-associated genes were differentially expressed across immune-cell types, and hierarchical clustering identified several sets of genes sharing similar immune-cell-expression profiles. Genes within the same cluster tended to be associated with the same disease or diseases. For example, one cluster included genes encoding nucleic acid–binding proteins, such as *ILF3*, *CENPO*, *MED1* and *NCOA3*; these genes were associated with both SLE and psoriasis, in which early defects in clonal selection of B cells and T cells, respectively, have been implicated.

JIA-associated genome-wide significant loci included *PTPN22*, *IL2RA* and *IL21* as well as three of the five novel signals (*ADGRL2*, *TENM3* and *ANKRD30*). "In terms of JIA, the findings validate the importance of the IL-2 pathway in disease and how T-cell immunity is implicated in disease," says Eyre.

Network and protein–protein interaction analyses further supported the sharing of genetic risk factors across the 10 paediatric autoimmune diseases. Gene networks and pathways associated with several diseases



included CD40–CD40L, JAK–STAT activation, and type 1, 2 and 17 helper T-cell cytokine signalling pathways. "The shared associations with certain genes or genetic variants across multiple autoimmune diseases allow us to think about patients with different autoimmune diseases more as subgroups or cohorts of individuals with specific variants," adds Hakonarson.

Many of the risk variants identified in the study encode proteins that are known or putative therapeutic targets, meaning the results could have implications for drug development and drug-repurposing approaches. "It would be anticipated that the subset of patients who harbour risk variants in gene 1 may be more likely to respond to drug A independent of which autoimmune disease they have, whereas patients with risk variants in gene 2 may be more likely to respond to drug B independent of the type of autoimmune disease they have, and so on," Hakonarson explains. "As a result, we would be personalizing therapies across multiple genetic diseases based on the genetic underpinnings these patients have."

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