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Unravelling the complex genetic regulation of immune cells

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Abstract

Genetic variation contributes to immune cell function. An unprecedented analysis of genetic associations with immune cell traits provides insights into the complex regulation of immune cells, reveals variants that coincidently influence immune traits and autoimmune disease risk, and offers specific therapeutic targets for these diseases.

The diversity of the immune system is a result of both environmental and genetic variation. Although critical in host defense, this diversity also contributes to immune dysregulation such as that exhibited during autoimmune disease. Thus, to better understand immune system function and dysfunction, identifying the genetic and environmental factors that regulate variation of immune cell traits is important. In a large study published in *Nature Genetics*[1], a team led by Francesco Cucca identified multiple genetic associations with immune cell traits and coincident associations with autoimmune risk loci, thus linking immune trait variants to disease phenotypes.

Although the influence of age, sex, cytomegalovirus infection and smoking on immune repertoire variation is well documented[2], the contribution of genetic factors to this variation is only beginning to be elucidated. In this latest study, Orrù et al.[1] measured a total of 731 immunophenotypes in a family based cohort of 3,757 individuals from the founder population of Sardinia, including 539 immune traits profiled by flow cytometry (such as cell counts and median fluorescence intensities of cell surface antigens), and 192 relative counts. With these high-resolution immune data, the team estimated that the proportion of phenotypic variation of the immune traits due to additive genetic effects (that is, the traits' heritability) had a median value of 37.0%. They found higher heritability for lymphoid cells and those involved in adaptive immunity, especially naive cell subsets (up to 47.0% for naive T cells), than for myeloid cells and those involved in innate immunity, whereas the observed variation among mature and differentiated cells (for example, 29.3% for terminally differentiated $CD4^+$ T cells) seemed to be more strongly influenced by environmental exposures. These results confirm the contribution of genetic factors to variation in immune cell phenotypes.

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Competing interests

The author declares no competing interests.

Five previous genome-wide association studies (GWAS) of immune cell traits were conducted to identify genetic variants associated with particular cellular immune phenotypes, resulting in the identification of close to 50 distinct loci associated with at least one immunological trait[3-7]. The study by Orrù et al.[1] greatly expanded on these findings by testing 22 million genetic variants for associations with 731 immune cell traits, unveiling 53 novel loci.

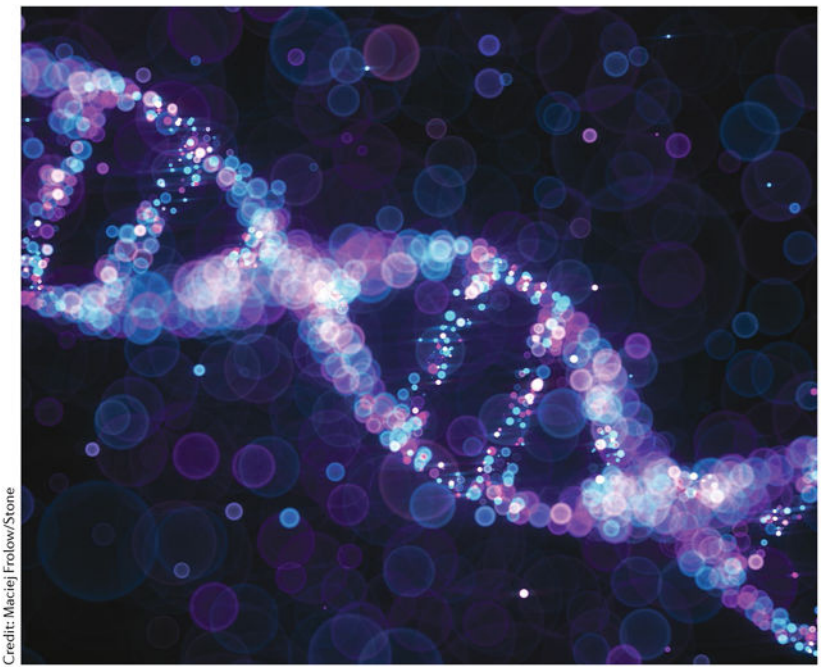
Given that the functional role of most genetic variants associated with immune-related diseases remains unknown, overlapping disease risk loci with immune cell trait loci might reveal 'coincident associations', thus suggesting potential causal relationships between a genetic variant, the involved immune cell subtypes and a disease. Of the 70 immune cell trait loci identified by Orrù et al.[1], 36 overlapped with reported GWAS disease risk loci. For example, an allele in the *SPATA48–IKZF1* region that was associated with decreased numbers of plasmacytoid dendritic cells (pDCs) colocalized with an allele also associated with a decreased risk of systemic lupus erythematosus (SLE) and might thus have a role in the deregulation of pDCs in SLE. An investigation into the potential therapeutic utility of the findings suggested that downregulation of pDCs via inhibition of the pDC-specific receptor BDCA2 (also known as CLEC4C), whose expression is regulated by the DNA-binding protein Ikaros (encoded by *IKZF1*), is a promising therapeutic route for SLE. Indeed, as the authors indicate, an anti-BDCA2 monoclonal antibody that inhibits the production of type I interferon and other inflammatory mediators is currently in a phase II trial for SLE therapy[8].

In another example, an allele in *CD40* that is associated with increased expression of CD27 on memory B cell subsets overlaps with an allele associated with increased risk of various autoimmune diseases (such as SLE, multiple sclerosis and inflammatory bowel disease), as well as a decreased risk of rheumatoid arthritis and Kawasaki disease. This same allele was associated with decreased expression of CD40. Orrù et al.[1] found evidence implicating inhibition of CD27 on memory B cells as a therapeutic strategy in SLE, inflammatory bowel disease and multiple sclerosis. By comparison, current therapies for SLE and multiple sclerosis are based on broad depletion of B cells, rather than depletion of memory B cell subsets.

This study[1] clearly shows that the regulation of immune cell traits is complex. In some cases, multiple independent loci influenced the expression of a given surface marker in different cell subtypes with distinct effects on disease risk. For example, different independent variants at the *IL2RA* locus were associated with either higher or lower expression of CD25 in different cell subsets, and were associated with predisposition to or protection from different autoimmune diseases. Similarly, variation at the *CD28–CTLA4* locus was associated with reduced CD28 expression, especially in regulatory T cell subsets, whereas variants in *BACH2* were associated with increased CD28 expression in other T cell subsets. This intricate genetic regulation of immune cell levels and its consequences on immune-related diseases underscores the complexity of therapeutically targeting these diseases. Although most current biologic therapies for rheumatic diseases target a single protein, this study suggests that more efficacious and safer therapies ought to target multiple proteins to discriminate a particular cell subtype, or be based on targeted delivery of a drug to a specific cell type[1].

Despite the unprecedented number of immune cell phenotypes and genetic variants analysed, a limitation of this study[1] is the generalizability of the results to other groups and populations. The population of Sardinia is a founder population, which can help in identifying genetic variants that are rare or absent elsewhere but that occur at moderate frequencies in these populations. The discovery of new associations can elucidate causal mechanisms for immune phenotypes. However, it might be difficult to replicate such results in other populations because of the absence or rarity of the variant. In addition, nearly 80% of individuals in all reported GWAS are of European ancestry[9], which limits knowledge of genetic risk factors in ethnically diverse populations. This 'information disparity' affects the reliability of clinical genomic interpretation for under-represented populations[10] and can exacerbate health inequities[9]. The variation in prevalence of immune-related disorders along geographic gradients underscores the need to understand immune cell regulation in different populations and how the differences might affect the risk of disease.

Finally, this study[1] is a humble reminder that, despite extraordinary progress, much remains to be discovered about the genetic regulation of immune system variation. The effects of genetic and epigenetic variation, together with environmental exposures in individuals from different ancestries, must be elucidated for thorough understanding of the diversity of the immune system. The extensive data generated in this study[1] brings us closer to an improved understanding of the involvement of the immune system in human health and disease. This knowledge is expected to advance the field of medicine to use genomics in the transition to personalized medicine.



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