

Researchers identify genetic variants that impact immune cells' functioning

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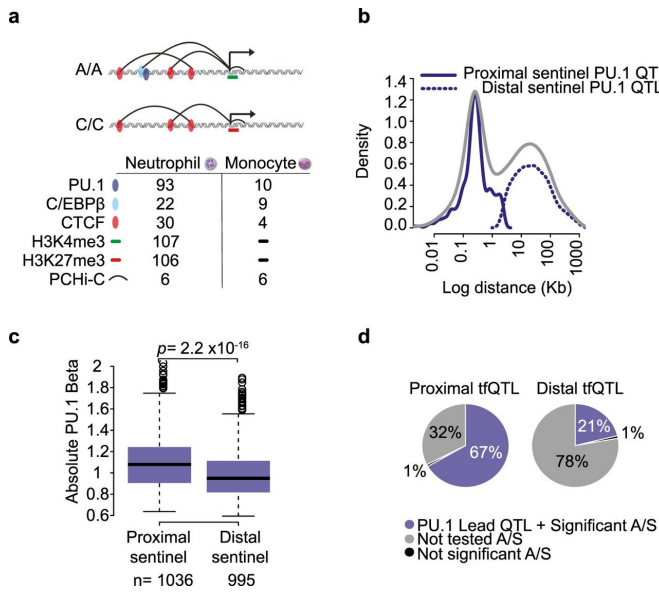


Fig. 1: Properties of PU.1 transcription factor QTLs. From: Genetic perturbation of PU.1 binding and chromatin looping at neutrophil enhancers associates with autoimmune disease. Credit: *Nature Communications* (2021). DOI: 10.1038/s41467-021-22548-8

Researchers have combined genome-wide sequencing and functional profiling of immune cells to understand more about the impact of genetic variants on disease.

Certain genetic variants that cause modified protein binding in immune cells, are also seen in those at high risk of some autoimmune diseases, new research has found.

Scientists from the Wellcome Sanger Institute, Josep Carreras Leukemia Research Institute in Spain, and the MRC London Institute of Medical Sciences (LMS) found that certain genetic variants, which alter the binding ability of a protein called PU.1 in neutrophils, are also found to be associated with autoimmune disease

susceptibility.

This new study, published in *Nature Communications* (16 April 2021), builds on previous research called BLUEPRINT. BLUEPRINT revealed how variation in blood cells' characteristics and numbers can affect a person's risk of developing complex diseases such as heart disease, and autoimmune diseases including rheumatoid arthritis, asthma, coeliac disease and type 1 diabetes.

This new research has provided more mechanistic detail on how PU.1 and neutrophils are impacted by genetic variation and has provided researchers a list of candidate genes that would be of interest for further research to investigate if these have a causal effect on the development of autoimmune disease.

Differences in individuals, such as risk of disease, can be influenced by a number of factors. While some of this variation is influenced by the environment and external factors such as diet, there is a substantial component driven by genetics. However, most variation is not driven through the function of a single gene but rather the sum of many subtle changes in genes or regions that control gene activity.

Previously, BLUEPRINT ran large-scale genome-wide association studies (GWAS) to investigate which genetic differences are linked to changes in blood cells and if these have a link to disease. GWAS are powerful tools for identifying regions of the genome associated with human variation and diseases. However, GWAS doesn't look at specific cell types, which makes it difficult to determine the genes that certain regions code for and the cell types they regulate.

In this new research, scientists from the Wellcome Sanger Institute, Josep Carreras Leukemia Research Institute, Spain, and the MRC London

Institute of Medical Sciences (LMS), combined previous GWAS data with in-depth functional analysis of neutrophils ? a type of immune cell that make up 80 percent of the white blood cells in the body.

They found that the genetic variants that are associated with an increased risk of autoimmune disease also have an impact on binding of a certain protein in neutrophils, known as PU.1. Some genetic variants made PU.1 unable to bind to neutrophil DNA, which led to subsequent changes in gene expression and neutrophil behavior.

While further research is needed to see if this change in the ability of PU.1 to bind directly causes certain autoimmune diseases, this research provides further understanding about the impact of these genetic variants on the cells in the body. In addition to this, the researchers suggest a list of candidate [genes](#) that could hold further information about the genetic causes of autoimmune [disease](#).

More information: Stephen Watt et al. Genetic perturbation of PU.1 binding and chromatin looping at neutrophil enhancers associates with autoimmune disease, *Nature Communications* (2021). [DOI: 10.1038/s41467-021-22548-8](https://doi.org/10.1038/s41467-021-22548-8)

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