How blood cell genetic variations impact on common diseases

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In a guest blog, Professor David Roberts from the Nuffield Division of Clinical Laboratory Sciences at Oxford University explains the role of non-DNA genetic information in disease and development.

One of the great mysteries in biology is how the many different cell types that make up our bodies are derived from a single cell and from one DNA sequence, or genome. We have learned a lot from studying the human genome, but have only partially uncovered the processes underlying cell determination and susceptibility to different diseases.

The differences in the number of cells and their function between people are partly dependent on the genetic variation in the DNA code. The identity of each cell type is largely defined by an instructive layer of molecular annotations on top of the genome – the epigenome – which acts as a blueprint, unique to each cell type and developmental stage. Unlike the genome, the epigenome is modified as cells develop and in response to changes in the environment.

We have helped compile a landmark global study to characterise the role of not only intrinsic genetic variants, but also epigenetic molecular tags that decorate our DNA code, in the formation of blood cells. The research, published as part of a suite of articles, delves into these genetic variations in blood cells and how they influence common diseases such as arthritis.

Defects in the factors that read, write and erase the epigenetic blueprint are involved in many diseases. Comprehensive analysis of the role of genetic variation, combined with the knowledge of the epigenomes of healthy and abnormal cells, will facilitate new ways to diagnose and treat various diseases, and ultimately lead to improved health outcomes.

Our team at National Health Service Blood and Transplant at the University of Oxford, collaborated with researchers at the University of Cambridge and the Sanger Institute to conduct an in-depth study of blood cell genetic profiles in more than 150,000 people. We integrated genetic and epigenetic information to define more than 2,500 previously undiscovered associations of genome regions with blood cell

characteristics and functions.

This study has increased the number of known genetic variants associated with blood cell types tenfold – creating the potential to develop new treatments for blood cell diseases, auto-immune diseases and arthritis. For example, we have found strong associations with the epigenetic markers of the turnover of red blood cells (or high reticulocyte counts) and cardiovascular disease, as well as associations of genetic markers of the eosinophil white blood cell numbers and rheumatoid arthritis. Here, the study has opened up new or overlooked pathways and mechanisms that lie behind these major diseases.

Our paper is one of a suite of 41 coordinated papers published by scientists from across the International Human Epigenome Consortium (IHEC), shedding light on these processes and taking global research in the field of genomics and epigenomics a major step forward.

The full research paper can be read in Cell, and the complete collection of papers from the consortium can be read here (volume 1) and here (volume 2).

More information: William J. Astle et al. The Allelic Landscape of Human Blood Cell Trait Variation and Links to Common Complex Disease, *Cell* (2016). DOI: 10.1016/j.cell.2016.10.042

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