Hidden genetic effects behind immune diseases may be missed, study suggests

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The role of genetics in the risk of having an immune disease could be missed in research, scientists suggest. Using a combination of stem cells and novel analytical tools, scientists at the Wellcome Sanger Institute and

their collaborators discovered that clues to the contribution of genetic variation to disease risk lie not only in the genes, but also in the molecular switches that control those genes.

The results, published today (29 January) in *Nature Genetics*, show for the first time how immune cells created from human induced pluripotent stem cells (HiPSCs) can model immune response variation between people.

Researchers discovered that the differences in immune responses due to genetic variation were only visible at certain stages of the experiment when the immune cells were in particular states, for example when they were activated.

In other states, only 'footprints' of the genetic variation effects could be seen. However by looking at two elements, the genes and regulatory regions - the molecular 'switches' that control the expression of those genes, the researchers were able to identify the true impact of genetic differences on immune response.

The results suggest that the actual effects of genetic variation on immune response are often hidden if not searched for thoroughly.

An understanding of the role genetic variants play in helping our immune systems fight diseases is an important step towards better targeted therapies.

Dr Dan Gaffney, senior author from the Wellcome Sanger Institute, said: "We have found that the impact of genetic variants on how people's immune cells respond to a pathogen like Salmonella are condition-specific - they are only visible at certain stages of infection. This means that the effects of genetic differences in immune disorders could be missed in research, if scientists aren't studying both the genes and their

control regions, the regulatory elements, of immune cells at all stages of an infection."

In the study, scientists differentiated human induced pluripotent stem cells into white blood cells called macrophages. The macrophages were then studied in four different states: unstimulated, after 18 hours of stimulation with a signalling molecule interferon-gamma, after five hours infection with Salmonella, and after interferon-gamma stimulation followed by Salmonella infection.

Dr Kaur Alasoo, previously from the Wellcome Sanger Institute and now from the University of Tartu, Estonia, said: "A benefit of using stem cells rather than pre-existing blood cells is they're very flexible, and enabled us to study the effects of stimulation at two different levels. We analysed which genes in the genome were expressed during each stage of infection, but also looked at the activity of enhancers - the molecular 'switches' that controlled the expression of those genes. This novel combination of tools enabled us to see otherwise hidden effects of genetic variation on immune response."

The team also discovered that genetic variation impacts on the readiness of the immune cells to tackle an infection. In particular, some individuals' immune cells were ready to deal with the Salmonella infection, whereas other individuals' macrophages were less ready and took longer to respond. This level of 'readiness' was due to a phenomenon known as enhancer priming, where some of the switches were already turned on in the unstimulated cells to facilitate a quicker response. In some cases, the immune cells could be overly eager and this can lead to an inflammatory response associated with immune disorders.

Professor Gordon Dougan, from the Wellcome Sanger Institute, added: "If the genetic variant being studied is associated with disease, such as an immune disorder, one needs to be sure of which gene the variant is

affecting in order to develop an effective therapy. This may only be visible in a small time-window of the infection. These results offer important new insights into studying the mechanisms behind infection and disease."

More information: Kaur Alasoo et al. (2018) Shared genetic effects on chromatin and gene expression indicate a role for enhancer priming in immune response. *Nature Genetics*. DOI: 10.1038/s41588-018-0046-7

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