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Genetic variation is key to fighting viruses

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Using a genome-wide association study, EPFL scientists have identified subtle genetic changes that can cause substantial differences to how we fight viral infections.

When infected with a virus, the response of our immune systems varies widely from person to person. This variation is of great concern, as these differences can determine clinical outcome as well as effectiveness of vaccinations. Comparing the genomes of over 2000 people, scientists from EPFL and the Max Plank Institute have pinpointed a genetic link behind immune variations. Published in the *American Journal of Human Genetics*, the work connects genetics to antiviral immunity while offering a new path for studying this relationship in other medical contexts.

Studying genomes to spot correlations

The mapping of the human genome - the complete set of DNA of a single person - in 2001 opened up an immensely complex network of genetic information. Biologists today have tools that can study whole genomes instead of individual genes, which has proven very useful when trying to identify which gene or genes are behind complex biological functions, such as immunity.

One of these tools is called a "genome-wide association study". In these studies, computers are used to rapidly scan the genomes of many people to find patterns of genetic variations associated with a particular biological function or a disease.

Genomes, viruses and the immune system

The lab of Jacques Fellay at EPFL performed a genome-wide association study on over 2000 people to uncover the genetic elements that underlie the immune response to viruses. The study, led by postdoc Christian Hammer, looked at fourteen common viruses against which antibodies are developed following natural infection or vaccination. Each one of the people tested had developed varying degrees of immunity against each virus, which can be assessed by measuring the presence and concentration of a particular antibody in their blood.

Using this information, the EPFL scientists also looked at the genetic data from each patient to identify correlations of about 6 million common variants across the whole genome with the degree of immune response to each virus. This complex analysis generated masses of digital data, which had to be processed in specialized computer systems at the Vital-IT Group facilities in Lausanne.

Of the fourteen viruses, the study found "hits" on four: influenza A virus, Epstein-Barr virus, JC polyomavirus, and Merkel cell polyomavirus. There seemed to be a strong connection between immune responses to these and genetic variations across a cluster of genes that are known to be involved with the immune response to viruses.

Specifically, these genes - all located on the same chromosome - produce a group of proteins whose job is to attach to viruses and expose specific parts of them to our immune cells, which fight the virus in response. The genetic variations on the genes directly affect the structure of the proteins, and finally impact their ability to present the virus properly and trigger an immune response.

Interestingly, the study also found that the same genetic variant can affect immune responses differently depending on the virus. For

example, a variation can decrease immunity against influenza A but increase it for Epstein-Barr virus. The same variants are already known to also play a role in autoimmune diseases that could be modulated by viruses.

But the scientists emphasize that while the study shows correlations, it does not imply causation, which has to be investigated in the future. Nonetheless, the work opens a novel way for exploring, understanding and perhaps even boosting immunity with treatments guided by genomic information.

More information: Hammer C, Begemann M, McLaren PJ, Bartha I, Michel A, Klose B, Schmitt C, Waterboer T, Pawlita M, Schulz TF, Ehrenreich H, Fellay J. Amino Acid Variation in HLA Class II Proteins Is a Major Determinant of Humoral Response to Common Viruses. *American Journal of Human Genetics* 05 November 2015. DOI: 10.1016/j.ajhg.2015.09.008

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