An immune cell 'fingerprint' reveals path for better treatment of autoimmune diseases

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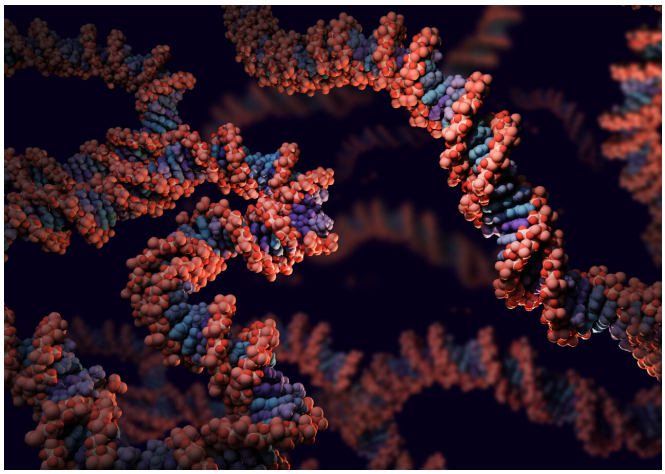


Strands of DNA. Credit: Dr. Kate Patterson, Garvan Institute of Medical Research

Most autoimmune diseases are easy to diagnose but hard to treat. A paper published today in *Science* proposes using your unique immune cell fingerprint to rapidly identify which treatments will work for your autoimmune disease.

"We analyzed the genomic profile of over one million cells from 1,000 people to identify a fingerprint linking genetic markers to diseases such as multiple sclerosis, rheumatoid arthritis, lupus, type 1 diabetes, spondylitis, inflammatory bowel disease, and Crohn's disease," says Professor Joseph Powell, joint lead author at the Garvan Institute of Medical Research. "We were able to do this using single cell sequencing, a new technology that allows us to detect subtle changes in individual cells," he says.

The discovery could help individuals find tailored treatments that work for them and guide the development of new drugs.

The study by researchers in Sydney, Hobart, Melbourne, Brisbane and San Francisco helps us understand why some treatments work well in some patients, but not in others. It's the largest study to date to link disease-causing genes to specific types of immune cells.

A trial is now underway in Sydney with Crohn's disease patients to predict which treatments will work for specific patients.

"Some autoimmune diseases can be notoriously difficult to treat," says Professor Powell.

"Because of our immune system's complexity, and how vastly it varies between individuals, we don't currently have a good understanding of why a treatment works well in some people but not in others," he says.

The study links specific genes and immune cell types to an individual's disease, including multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, type 1 diabetes and Crohn's disease.

This means an individual's unique genetic profile could be used to deliver treatments tailored to precisely tame their immune system.

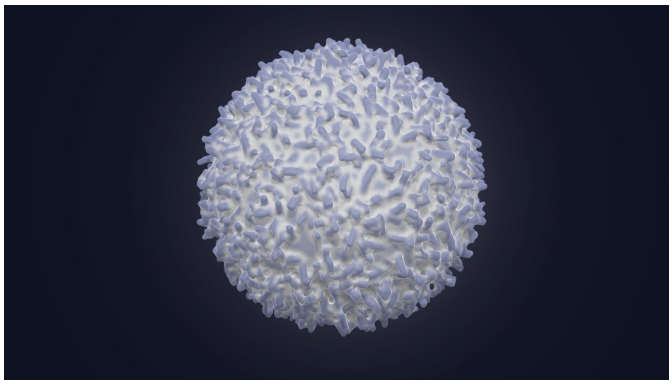
"Our data also provides a new avenue for narrowing down potential drug targets. The potential health and economic impacts of this research are enormous," says Professor Alex Hewitt, joint lead author and clinician-researcher at the University Of Tasmania's Menzies Institute for Medical Research.

"Most rare genetic diseases are like a major car accident in the body—they are generally easy to identify and locate where they occur in the genome. But immune diseases are often more like traffic congestion, where genetic changes that hold up traffic are harder to specifically pinpoint. This study has helped us identify the trouble spots," says Professor Hewitt.

"The greatest insight from this work will be identification of therapeutic targets and defining sub-populations of immune disease, which can then refine clinical trials to assess drug effectiveness," he says.

Our bodies' immune systems are designed to fight external threats, but autoimmune diseases occur when our immune systems take aim at our own healthy cells. They affect about one in 12 Australians, are incurable and require lifelong treatments to minimize the damage.

Often, patients will trial many different treatments before finding one that works for them.



B cell. Credit: Dr. Ofir Shein-Lumbroso

"Some medications may be very effective in only 15% of patients, so are not recommended as a first-line treatment," says Dr. Seyhan Yazar, co-first author of the study. "We now have a way to link treatment response back to an individual's immune genetics—and to potentially screen for that 15% of patients before a clinician even administers a treatment."

The researchers say their data could lower the risks associated with developing new treatments.

"Pharmaceutical companies may have hundreds of targets and have to make decisions about which they will take forward to Phase I clinical trials, knowing that 90% of potential drug candidates fail during clinical development," says Dr. José Alquicira-Hernández, co-first author and researcher at the Garvan Institute.

"Understanding which cell types are relevant for a particular disease is key for developing new drugs."

A million cells reveal complexity and provide certainty

The study provides unique insights by looking at genes in individual immune cells on an unprecedented scale. It analyzed the genomics of more than one million individual immune cells from around 1,000 healthy individuals, exploring 14 different types of immune cells in total.

This individual approach paints a far clearer picture than previous studies which analyzed combined cells in a blood sample.

"The problems with bulk RNA analysis is that we only observe an averaged signal. But there is vast variation in cell functions and cell types that allow the body to defend against attack," explains says Dr. Yazar. "Average analysis doesn't reflect what happens in the full variety of immune cells."

Integrating into clinical trials

The findings have led to clinical trials. "We are working on a study of Crohn's disease in collaboration with St George Hospital that will determine how a patient's immune genotype affects their response to different treatments and are looking to establish new trials in a range of autoimmune diseases," says Professor Powell.

"It is a significant milestone of Garvan's pioneering OneK1K study aimed at showing how genetics contribute to the risk of immune disease at a cellular level."

More information: Seyhan Yazar et al, Single-cell eQTL mapping identifies cell type specific genetic control of autoimmune disease, *Science* (2022). DOI: 10.1126/science.abf3041. www.science.org/doi/10.1126/science.abf3041