Genetic study gives extensive insights into severe COVID-19

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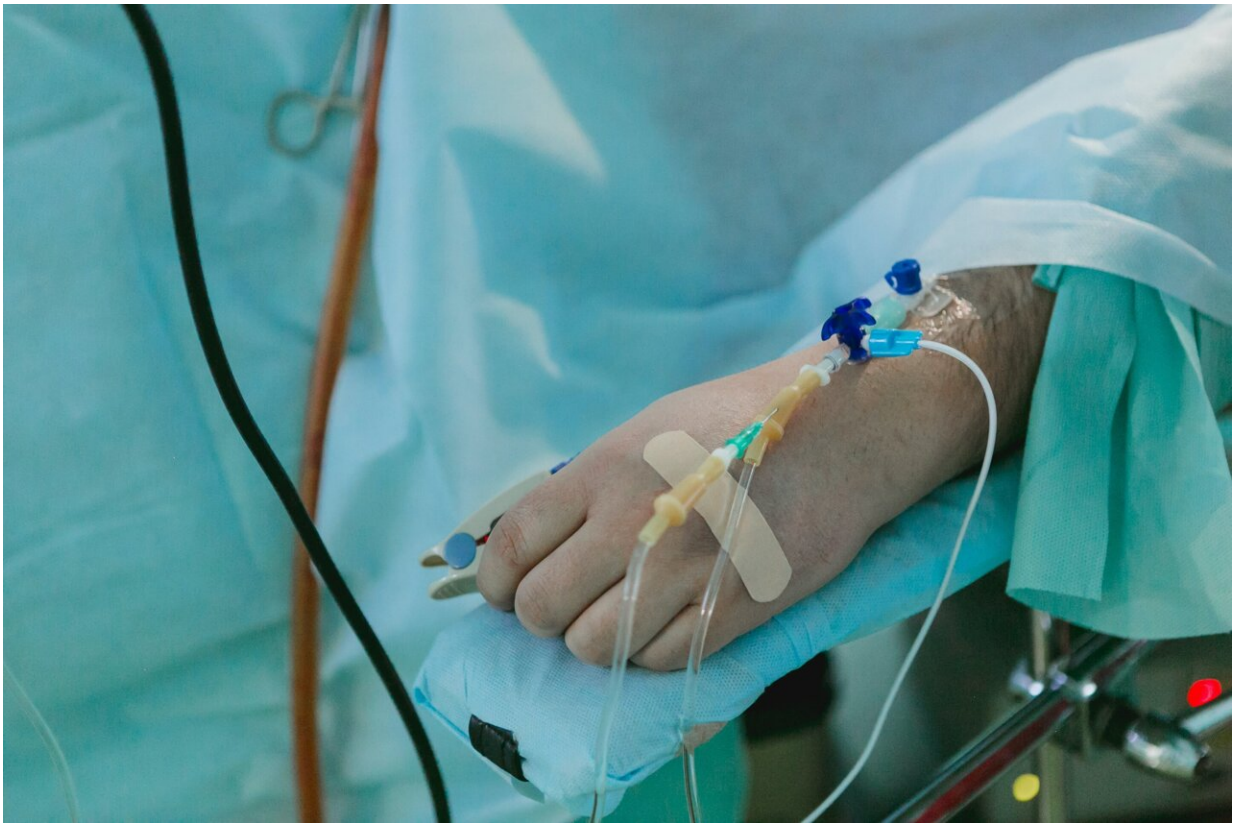

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The world's largest study of the genetics of critical COVID-19, involving more than 57,000 people, has revealed fresh details about some of the biological mechanisms behind the severe form of the disease.

Some 16 new genetic variants associated with severe COVID-19, including some related to blood clotting, immune response and intensity of inflammation, have been identified.

These findings will act as a roadmap for future efforts, opening new fields of research focused on potential new therapies and diagnostics with pinpoint accuracy, experts say.

Researchers from the GenOMICC consortium—a global collaboration to study genetics in critical illness—led by University of Edinburgh in partnership with Genomics England, made these discoveries by sequencing the genomes of 7,491 patients from 224 intensive care units in the UK.

Their DNA was compared with 48,400 other people who had not had COVID-19, participants in Genomics England's 100,000 Genomes Project and that of a further 1,630 people who had experienced mild COVID.

Determining the whole genome sequence for all participants in the study allowed the team to create a precise map and identify genetic variation linked to severity of COVID-19. The team found key differences in 16 genes in the ICU patients when compared with the DNA of the other groups.

They also confirmed the involvement of seven other genetic variations already associated with severe COVID-19 discovered in earlier studies from the same team.

The findings included how a single gene variant that disrupts a key messenger molecule in immune system signaling—called interferon alpha-10—was enough to increase a patient's risk of severe disease.

This highlights the gene's key role in the immune system and suggests that treating patients with interferon—proteins released by immune cells to defend against viruses—may help manage disease in the early stages.

The study also found that variations in genes that control the levels of a central component of blood clotting—known as Factor 8—were associated with critical illness in COVID-19.

This may explain some of the clotting abnormalities that are seen in severe cases of COVID-19. Factor 8 is the gene underlying the most common type of hemophilia.

Professor Kenneth Baillie, the project's chief investigator and a Consultant in Critical Care Medicine at University of Edinburgh, said: "Our latest findings point to specific molecular targets in critical COVID-19. These results explain why some people develop life-threatening COVID-19, while others get no symptoms at all. But more importantly, this gives us a deep understanding of the process of disease and is a big step forward in finding more effective treatments.

"It is now true to say that we understand the mechanisms of COVID better than the other syndromes we treat in intensive care in normal times—sepsis, flu, and other forms of critical illness. COVID-19 is showing us the way to tackle those problems in the future."

Professor Sir Mark Caulfield from Queen Mary University of London, formerly Chief Scientist at Genomics England and co-author on this study, said: "As COVID-19 evolves, we need to focus on reducing the number of people getting seriously ill and being hospitalized. Through our whole genome sequencing research, we've discovered novel gene variants that predispose people to severe illness—which now offer a route to new tests and treatments, to help protect the public and the NHS from this virus."

Dr. Rich Scott, Chief Medical Officer at Genomics England, said: "Strategically, we're at a point where genomic science is becoming an integral part of the national infrastructure in routine healthcare. This study illustrates the value of whole genome sequencing to detect rare and common variants that influence critical illness requiring intensive care. It represents a major leap forward in our understanding of how our genetic makeup influences severe illness with COVID-19."

"All those involved in the study went to great efforts to engage with all communities within the UK—including groups that have historically been under-represented in medical studies. The inclusive element of our work has generated meaningful results for everyone in the country."

Lord Kamall, Minister for innovation at the Department of Health and Social Care (DHSC), said: "Clinical research has been vital in our fight against COVID-19 and the UK's innovation is enabling us to transform our health service and ensure the NHS is able to deliver world-class care.

"This research is an important step forward in better understanding how COVID-19 impacts certain people, allowing us to take the necessary action to protect the most vulnerable and save lives."

The findings have been published in *Nature*.

GenOMICC (Genetics of Susceptibility and Mortality in Critical Care) started in 2015 as an open, global consortium of intensive care clinicians dedicated to understanding genetic factors influencing outcomes in intensive care from diseases such as SARS, flu and sepsis.

The ground-breaking 100,000 Genomes Project was established in 2014 to sequence 100,000 genomes from people with a rare disease or cancer. The Project was completed in 2018 and paved the way for the creation of a new genomic medicine service for NHS England, transforming

patient care by bringing advanced diagnosis and personalized treatments.

More information: The authors can be contacted via the University of Edinburgh press office:, Whole genome sequencing reveals host factors underlying critical Covid-19, *Nature* (2022). DOI: 10.1038/s41586-022-04576-6. www.nature.com/articles/s41586-022-04576-6

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