NEWS

Study reveals why some otherwise healthy COVID patients end up in ICU

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The 'staggering' link between coronavirus severity and an immune system flaw may also show why men tend to have more serious disease.

The studies included patients who were admitted to the intensive care unit (ICU) despite being in their 20s and otherwise healthy.

Findings in two recently-published papers have helped explain why some people develop much more severe COVID-19 disease than others in their age group.

The research, published in *Science*, found that more than 10% of healthy people who develop severe COVID-19 produce misguided antibodies that attack the patient's own immune system, rather than the invading virus, while at least another 3.5% carry genetic mutations that impair their immune response.

Associate Director at the Hudson Institute of Medical Research, Professor Paul Hertzog, said the papers carry impo messages for understanding the disease, as well as screening tests for targeted therapy and potentially vaccinatio

'Together they implicate defects in the protective interferon system in a staggering 14% of severely ill COVID-19 patients,' he said

'Interferons are the body's premier antiviral compounds and it is likely that further studies will uncover even more defects that prevent the body mounting an effective antiviral response.'

Study participants included various nationalities from Asia, Europe, Latin America, and the Middle East, as well as patients who required admission to the intensive care unit (ICU) despite being in their 20s and otherwise healthy.

The findings are the first results stemming from the COVID Human Genetic Effort, an ongoing international project spanning more than 50 sequencing hubs and hundreds of hospitals around the world, including the Murdoch Children's Research Institute (MCRI).

MCRI's Professor John Christodoulou, who is co-leading the Australian arm of the project, said the two new papers also provide a potential explanation for why men appear to be more vulnerable to severe COVID than women.

'The way SARS-CoV-2 affects people differently has been puzzling. The virus can cause a symptom-free infection and go away quietly, or it can kill in a few days,' he said.

'The researchers sequenced genes for 13 proteins that are very important for protecting against viral infections and in 3.5% of individuals with severe COVID-19 pneumonia, changes in a number of these genes were identified. The changes compromised their ability to protect against COVID-19 infection by impairing patients' ability to make type I interferon.

'Also 10% of individuals with severe COVID-19 infection had auto-antibodies to type I interferon, neutralising the early protective effect of innate immunity.

'Importantly, 95% of these individuals were men, which might explain at least some of the sex differences we see in COVID-19 infection, which tends to affect males more severely.'

While potentially providing the first molecular explanation as to why more men than women die from COVID, Professor Jean-Laurent Casanova, Head of the St Giles Laboratory of Human Genetics of Infectious Diseases at Rockefeller University, believes the findings may also lead to potential new treatments.

'These findings provide compelling evidence that the disruption of type I interferon is often the cause of life-threatening COVID-19,' he said. 'At least in theory, such interferon problems could be treated with existing medications and interventions.'

Head of the Oceania node of the COVID Human Genomic Effort and co-author of one of the papers, Professor Stuart Tangye, explains how.

'Interferons are small proteins that are made by many cell types very quickly following infection by different pathogens, including viruses,' he said.

'Both studies suggest that a defect in type I interferon immunity underlies life-threatening COVID-19 pneumonia ... [and] reveal type I interferons as a central requirement for strong immunity against SARS-CoV-2 infection and COVID-19.

'The findings raise the possibilities of exploring new potential treatment of COVID-19, such as "diluting" the effects of auto-antibodies via plasmapheresis or infusing type I IFNs as anti-viral agents.'

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