Study links key gene to protection from severe illness and death from COVID infections in men under age 75

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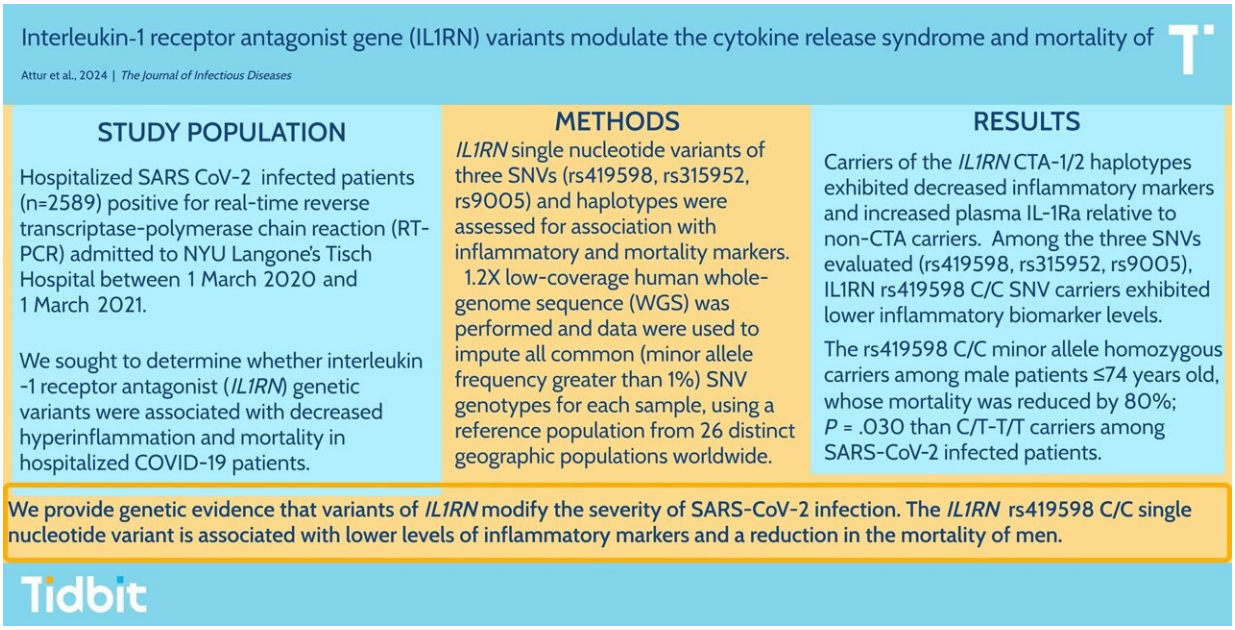

Graphical Abstract. Credit: *The Journal of Infectious Diseases* (2024). DOI: 10.1093/infdis/jiae031

A certain variant of a key anti-inflammatory gene protects men under age 75 from severe illness and death when hospitalized from COVID-19, a genetic analysis of their blood shows.

According to the study authors, the protective gene in question, an

interleukin-1 receptor antagonist (IL1RN) variant, appears to tamp down inflammation. Inflammation is the body's normal reaction to infection, but when unchecked, inflammation can go too far and damage tissues as part of many diseases, including in severe cases of infection with the pandemic virus SARS-CoV-2.

Published in *The Journal of Infectious Diseases*, the study showed that 124 men between the ages of 19 and 74 who possessed the IL1RN variant, called rs419598, were less likely to become severely ill after hospitalization for COVID-19, and 80% less likely to die from the disease.

IL1RN is expressed naturally in the body. Different types of interleukin genes are known to dial inflammation up or down in the context of arthritis, and researchers say the results of the current study suggest that a similar dynamic influences the interleukin-1-related inflammation seen in COVID-19 patients.

The findings, from researchers at NYU Grossman School of Medicine, stand out because historically, more men than women are known to die from COVID-19, and the IL1RN rs419598 variant appears to protect only men up to age 74 selectively, but not beyond that as age-related chronic illnesses unfold.

The research team used sequencing technologies for the study to determine the presence of specific genes or variations in the letter code that makes up genes in blood samples from 2,589 men and women hospitalized for COVID-19 at NYU Langone's Tisch Hospital in Manhattan from March 2020 to March 2021.

More than half of the men and women in the study were older than age 60 and obese, factors that are known to increase the risk of death from the viral infection. Overall, more men than women (240 men, at 60.5%,

and 157 women, at 39.5%) died from their disease, with women 20% less likely to die than men.

"Our study results show that among hospitalized patients, while women are still overall less likely than men to die from COVID-19, those men age 74 and younger who possess the IL1RN gene variant rs419598 are much less likely to suffer the severe inflammation tied to SARS-CoV-2 infection and less likely to die from the disease," said study co-lead investigator and molecular biologist Mukundan Attur, Ph.D. Attur is an associate professor in the Department of Medicine at NYU Langone Health.

Among the study's other findings was that average blood levels of the anti-inflammatory protein IL-1Ra, coded by IL1RN, were 14 times higher in 181 hospitalized men than in healthy male study controls from the general population and 10 times as high in 178 hospitalized women than in healthy females. However, researchers say the increased levels of IL-1Ra in women did not result in any statistically significant reductions in death.

"Our analysis offers substantial evidence of the biological link between the severe inflammation seen in SARS-CoV-2 and that which occurs in rheumatoid arthritis," said study senior investigator Steven Abramson, MD, the Frederick H. King Professor of Internal Medicine at NYU Langone.

Abramson, a rheumatologist who also serves as chair of the Department of Medicine and chief academic officer at NYU Langone, says previous research has shown that such rheumatoid inflammation is lower in people who possessed one of the three IL1RN variants analyzed in the study.

More importantly, Abramson says, the new research suggests that

restraining the interleukin-1 biological pathway, which is in part tamped down by the anti-inflammatory protein IL-1Ra, could help prevent the severe inflammation seen in SARS-CoV-2 infection. Further research, he says, is warranted into whether IL-1-inhibiting therapies, such as the IL1 receptor antagonists anakinra, canakinumab, and rilonacept, are effective against COVID infection.

Abramson already has plans to investigate if the IL-1 pathway plays a role in long COVID, when people experience new or lingering symptoms, such as fatigue and "brain fog," months after recuperating from their initial infection.

Abramson points out that the new study adds to the growing scientific evidence about the biological factors that contribute to gender differences seen in deaths from COVID-19, which are known to vary widely across the United States.

More information: Steven B. Abramson et al, Interleukin-1 receptor antagonist gene (IL1RN) variants modulate the cytokine release syndrome and mortality of SARS-CoV-2, *The Journal of Infectious Diseases* (2024). DOI: 10.1093/infdis/jiae031

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