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How a common gene variant influences your risk of severe illness from COVID-19

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Anew study led by Yale researchers has found that a common genetic variant that occurs in nearly 20% of individuals influences both susceptibility to COVID-19 and the development of severe disease.

"Knowledge of this gene variation can identify patients who need to be monitored and treated more aggressively to prevent severe illness," said the study's lead author Jenny Shin, MD, Ph.D., assistant professor of medicine in the Section of Rheumatology, Allergy & Immunology in the internal medicine department of Yale School of Medicine.

Variant forms of the gene are also associated with complications of different infectious and autoimmune disorders, said Richard Bucala, MD, Ph.D., Waldemar Von Zedtwitz Professor of Medicine (rheumatology), professor of pathology and of epidemiology (microbial diseases), and the study's organizer. "The new findings validate the importance of natural variation in our genes in different stages of COVID-19 infection," Bucala said.

The role of inflammation in the progression to severe COVID-19

The authors relate their findings in the article, "MIF is a Common Genetic Determinant of COVID-19 Symptomatic Infection and Severity," published in *QJM: An International Journal of Medicine*.

The findings are the culmination of a multinational, retrospective case control study of 1,177 patients from three tertiary medical centers in the United States and Europe that examined if common genetic variants in the immune cytokine macrophage migration inhibitory factor (MIF) were associated with COVID-19.

The authors first assessed susceptibility to infection by comparing MIF gene frequencies in COVID-19 patients with a pre-pandemic control group of 637 healthy subjects. Those with a high inflammatory variant of the MIF gene were found to be less likely to be diagnosed with COVID-19. Among all subjects with COVID-19, however, those with

the high inflammatory MIF variant were nearly 3-fold more likely to require hospitalization, indicating an underlying role for inflammation in the progression to severe COVID-19 illness.

"This genetic predisposition to severe COVID-19 occurs in 19% of individuals, and the 2.9 fold higher risk of hospitalization after diagnosis occurs independently of age, sex, or other factors," said Shin. "Knowledge of the gene variant could identify patients who need to be monitored or treated more aggressively to prevent severe illness and hospitalization. The genetic information also could benefit the prioritization of health resources in different parts of the world in future pandemics."

Yale clinicians had suspected a role for MIF in severe COVID-19 at the outset of the pandemic. Maor Sauler, MD, associate professor of medicine and Geoffrey Chupp, MD, professor of medicine in the Section of Pulmonary, Critical Care & Sleep Medicine, had initiated a clinical phase II trial for severe COVID-19 of a MIF antagonist discovered by Yale pharmacologists before the genetic results were known.

More information: Junghee J Shin et al, MIF is a Common Genetic Determinant of COVID-19 Symptomatic Infection and Severity, *QJM: An International Journal of Medicine* (2022). DOI: 10.1093/qjmed/hcac234

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