

Rare genetic variant puts some younger men at risk of severe COVID-19

March 23 2021



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A study of young men with COVID-19 has revealed a genetic variant linked to disease severity.

The discovery, published recently in *eLife*, means that men with severe

[disease](#) could be genetically screened to identify who has the variant and may benefit from interferon treatment.

For most people, COVID-19, the disease caused by the virus SARS-CoV-2, causes only mild or no symptoms. However, severe cases can rapidly progress towards respiratory distress syndrome.

"Although older age and the presence of long-term conditions such as cardiovascular disease or diabetes are known risk factors, they alone do not fully explain differences in severity," explains first author Chiara Fallerini, Research Fellow in Medical Genetics at the Department of Medical Biotechnologies, University of Siena, Italy. "Some younger men without pre-existing medical conditions are more likely to be hospitalized, admitted to intensive care and to die of COVID-19, which suggests that some factors must cause a deficiency in their [immune system](#)."

Recent research has suggested that genes controlling interferon are important in regulating the immune response to COVID-19. Interferon is produced by immune cells during viral infection. It works alongside molecules on the surface of immune cells called Toll-like receptors (TLR) which detect viruses and kickstart the immune response. "When a recent study identified [rare mutations](#) in a TLR gene, TLR7, in young men with severe COVID-19, we wanted to investigate whether this was an ultra-rare situation or just the tip of the iceberg," says co-senior author Mario Mondelli, Professor of Infectious Diseases at the Division of Clinical Immunology and Infectious Diseases, Fondazione IRCCS Policlinico San Matteo and University of Pavia, Italy.

The team studied a subset of 156 male COVID-19 patients younger than 60 years old, selected from a large multicentre study in Italy, called GEN-COVID, which started its activity on March 16, 2020. GEN-COVID is a network of more than 40 Italian hospitals coordinated by co-senior

author Alessandra Renieri, Full Professor of Medical Genetics at the University of Siena, and Director of Medical Genetics at Azienda Ospedaliero-Universitaria Senese, Siena, Italy.

The team first analyzed all the genes on the X chromosome of men with both mild and severe cases of COVID-19, and identified the TLR7 gene as one of the most important genes linked to disease severity. They then searched the entire GEN-COVID database, and selected for [younger men](#) (less than 60 years old). This identified rare TLR7 missense mutations in five of 79 patients (6.3%) with life-threatening COVID-19 and no similar mutations in the 77 men who had few symptoms. They also found the same mutation in three men aged over 60: two who had severe COVID-19 and one who had few symptoms—although the mutation found in the man with few symptoms had little effect on TLR function.

To link these mutations to the immune cell response, they treated white blood cells from recovered patients with a drug that switches TLR7 genes on. They found that the TLR7 genes were dampened down in immune cells from patients with mutations, compared to the TLR7 activity seen in normal [immune cells](#). They also found lower levels of interferon in the cells containing the mutation compared to normal white blood [cells](#). This confirmed that the mutations identified directly affect the control of interferon as part of the innate [immune response](#).

To confirm the impact of the mutations on COVID-19 response, the team studied two brothers, one with a mutation in an interferon gene and one without. The levels of interferon gene activity were much lower in the man with the missense mutation, compared with his brother. Moreover, the brother with the mutation had severe COVID-19, while his brother with normal interferon genes was asymptomatic.

"Our results show that young men with severe COVID-19 who have lost

function in their interferon-regulating [genes](#) represent a small but important subset of more vulnerable COVID-19 patients," says co-senior author Elisa Frullanti, Researcher of Medical Genetics at the University of Siena.

Co-senior author Alessandra Renieri adds: "These mutations could potentially account for [disease severity](#) in up to 2% of young men with COVID-19. We believe that screening for these [mutations](#) in men who are admitted with severe disease and promptly treating them with [interferon](#) could prevent more deaths."

More information: Chiara Fallerini et al, Association of Toll-like receptor 7 variants with life-threatening COVID-19 disease in males: findings from a nested case-control study, *eLife* (2021). [DOI: 10.7554/eLife.67569](#)

Provided by eLife

Citation: Rare genetic variant puts some younger men at risk of severe COVID-19 (2021, March 23) retrieved 5 May 2024 from <https://medicalxpress.com/news/2021-03-rare-genetic-variant-younger-men.html>

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