Mutation in TLR7 increases risk of severe COVID-19

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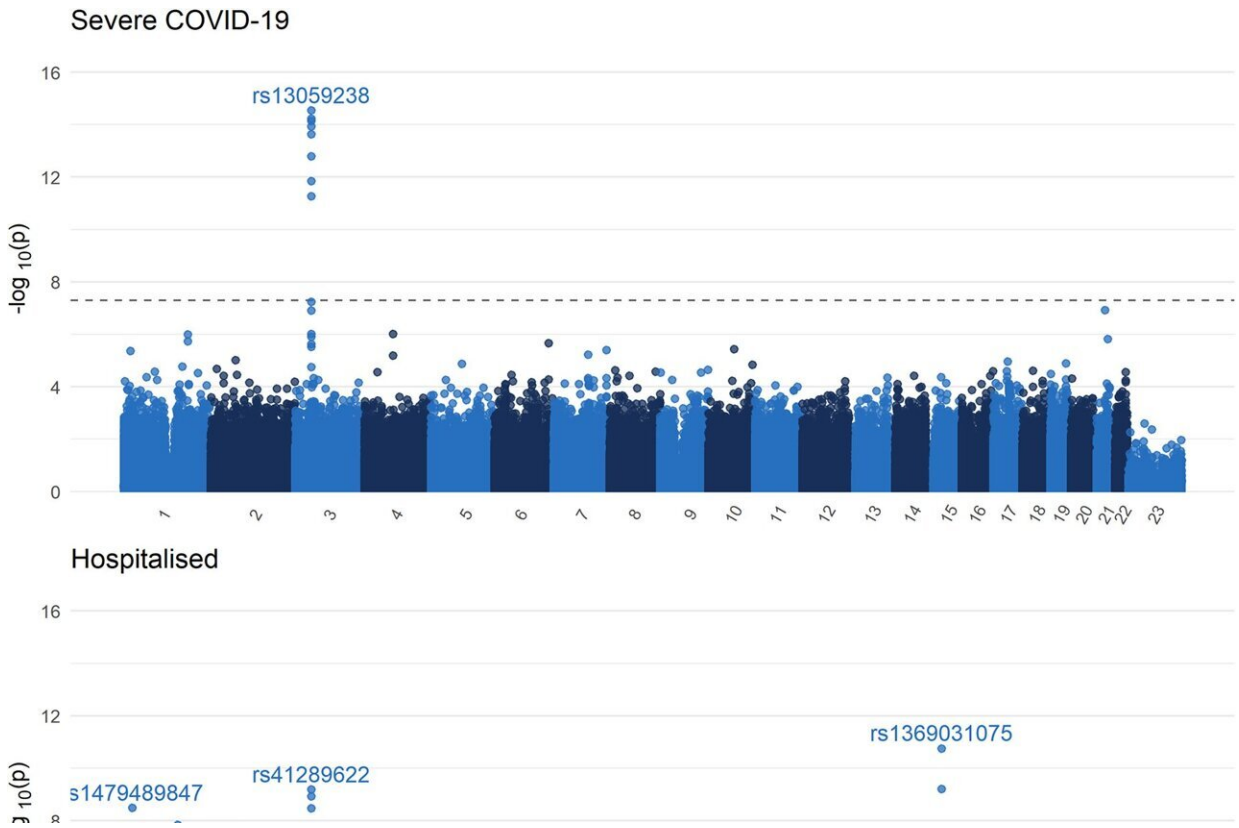

Single variant exome-wide association study Manhattan plot (MAF>0.1%). QQ-plot available in the S1 Fig. Black dashed line demarcates the genome-wide significance threshold (p^{-8}). Credit: *PLOS Genetics* (2022). DOI: 10.1371/journal.pgen.1010367

Rare gene mutations can significantly increase the risk of severe

COVID-19 disease. An international research team with significant contribution from the University of Bonn compared the genetic material of 5,085 people with severe COVID-19 and more than 570,000 controls. The results showed that alterations in the gene TLR7, which is important for the immune defense in humans, lead to infections with a severe course. The findings have now been published in the journal *PLOS Genetics*.

"TLR7 belongs to the Toll-like receptor family and recognizes pathogens, which is followed by subsequent activation of the innate immune system," says Dr. Kerstin Ludwig from the Institute of Human Genetics at the University Hospital Bonn. If loss of function of the TLR7 gene occurs due to mutations, the recognition of the SARS-CoV-2 virus may be impaired. This results in a lower defense by the immune cells—the virus receives less resistance.

The study confirms at the population level what was already known from individual cases: a genetically-mediated absence of TLR7 is a strong risk factor for severe COVID-19. On the one hand, this information can be used in the context of individual risk prediction. On the other hand, this finding now enables follow-up work on the pathological mechanism, the elucidation of which may be the basis for drug development for COVID-19.

21 contributions from 12 countries

The current study was only feasible because both genetic and clinical data were pooled from as many individuals with COVID-19 as possible. 21 studies from twelve countries contributed—including one from Germany. This German contribution came from the "DeCOI" initiative (www.decoi.eu) and was coordinated by Dr. Kerstin Ludwig of the University of Bonn together with Prof. Dr. Olaf Rieß (University of Tübingen) and Dr. Dr. Eva Schulte (Ludwig Maximilian University of

Munich).

"Together, we collected DNA from subjects at several German sites through the DeCOI consortium, generated genome sequence data with the help of the next-generation sequencing competence centers in Cologne, Tübingen and Bonn, and then merged the data in Bonn," reports Ludwig, who is a member of the ImmunoSensation2 cluster of excellence at the University of Bonn. Dr. Axel Schmidt from the Institute of Human Genetics then analyzed the large DeCOI dataset and coordinated the joint analysis with the other international groups.

Genetic risk factors

Shortly after the pandemic began, the international COVID-19 Host Genetics Initiative (COVID-19 HGI) formed, gathering cohorts worldwide to study host genetic factors. In recent months, scientists have already found several genetic risk factors that are common in the population. Individually, they do not cause disease, but do so in combination with other genetic and clinical risk factors, such as male sex, advanced age or obesity.

In contrast, it is expected that there are also patients in whom very rare variants confer a high risk for severe COVID-19. To investigate this, the WES/WGS subgroup of COVID-19 HGI was established. The analysis of WES/WGS data is accompanied by enormous amounts of data and bioinformatics requirements.

Moreover, these genetic data cannot simply be shared with global groups, but must be analyzed at individual study sites and then combined at a meta-level to avoid bias—for example, due to different technological methods. The researchers compared the genetic variants present in each gene of the entire genome in each cohort and their frequency between severely affected patients and control subjects.

"No less significant than the result, however, is the dimension of the international collaboration," Ludwig says. With impressive speed, she says, it was possible to get many nations involved in a large genetic project and to analyze genetic data together. The data set will be used for further studies.

More information: Guillaume Butler-Laporte et al, Exome-wide association study to identify rare variants influencing COVID-19 outcomes: Results from the Host Genetics Initiative, *PLOS Genetics* (2022). DOI: 10.1371/journal.pgen.1010367

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