

PRESS RELEASE

Large genetic study on severe COVID-19

Bonn researchers confirm three other genes for increased risk in addition to the known TLR7 gene

Bonn, July 24 - Whether or not a person becomes seriously ill with COVID-19 depends, among other things, on genetic factors. With this in mind, researchers from the University Hospital Bonn (UKB) and the University of Bonn, in cooperation with other research teams from Germany, the Netherlands, Spain and Italy, investigated a particularly large group of affected individuals. They confirmed the central and already known role of the TLR7 gene in severe courses of the disease in men, but were also able to find evidence for a contribution of the gene in women. In addition, they were able to show that genetic changes in three other genes of the innate immune system contribute to severe COVID-19. The results have now been published in the journal "Human Genetics and Genomics Advances".

Even though the number of severe cases following infection with the SARS-CoV-2 virus has decreased, there is still great interest in understanding why, at the height of the coronavirus pandemic, the infection was severe in some people but not in others. "This is important because it gives us information about the function and reaction of the immune system when it first comes into contact with a pathogen. If we have a better understanding of how severe courses of the disease develop, we can identify people at risk and protect them better or develop targeted therapies. We assume that the findings can be transferred at least in part to future pandemics," says corresponding author Prof. Kerstin Ludwig from the Institute of Human Genetics at the UKB, who is also a member of the Cluster of Excellence ImmunoSensation2 and the Transdisciplinary Research Area (TRA) "Life and Health" at the University of Bonn.

In addition to many possible reasons such as increased age or pre-existing conditions, some people's own genetic make-up can cause a severe course of the disease. Early work in the pandemic had already identified affected genes, most of which are involved in the innate immune response. The gene with the strongest evidence to date is the TLR7 gene, which was identified as the cause of the disease in two pairs of Dutch brothers with severe cases back in summer 2020. However, it was not yet known to what extent the effect of genetic changes in TLR7 is independent of other non-genetic risk factors, such as increased age or previous illnesses, and whether there are other genes in which so-called mutations significantly increase the risk of severe COVID.

Increased risk of severe Covid-19 lies in three other genes in addition to TLR7

In the recently published study, an international research group led by Prof. Ludwig looked at the gene sequences of 52 candidate genes, including TLR7, in a comparatively large patient sample. Through collaborations with various European groups, the Bonn researchers gained access to DNA material from 1,772 people with severe COVID-19 and 5,347 control

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individuals with unknown SARS-CoV-2 status from Spain and Italy - i.e. from regions where a very high incidence and high mortality rate was observed, especially at the beginning of the pandemic. All those affected were infected at a time when vaccinations were not yet available - these people therefore had no immune protection and were exposed to the virus virtually "unprepared".

In this large group of people, mutations that render the TLR7 gene non-functional were actually observed significantly more frequently in severely affected COVID-19 patients than in the control group. "This 'enrichment' was even stronger when only those affected people were considered who, due to their age and state of health, would not actually have had a high risk of a severe course. This means that certain mutations in this gene significantly increase the risk of severe progression," says first author and doctoral student at the Bonn Institute of Human Genetics Jannik Boos, who was in charge of the project. In addition to TLR7, the Bonn researchers were also able to identify mutations in the three other genes TBK1, INFAR1 and IFIH1 in the group of severely affected individuals.

Gender-specific differences in COVID-19 progression due to hereditary factors?

The Bonn researchers then took a closer look at TLR7 and found something interesting: the TLR7 gene is located on the X chromosome, of which men only have one copy, but women have two. "So if there is a loss of function of TLR7 on one copy, men no longer have a functioning gene - women, on the other hand, still have a healthy copy, so at least a little bit of functioning TLR7. It was therefore surprising for us that we also found TLR7 mutations more frequently in women with severe COVID-19 courses," says Dr. Axel Schmidt, who is a resident at the Institute of Human Genetics and in the Department of Neuropaediatrics at the UKB and led the study with Prof. Ludwig. Together with Prof. Alexander Hoischen's team from Radboudumc University Hospital in the Netherlands, the Bonn researchers found initial indications that the type of genetic changes is different in women: while in men the mutations lead to the absence of TLR7, in women the "broken" TLR7 versions appear to interact with the "healthy" copies and thus also influence their function. "We assume that TLR7 can also be impaired in women with severe COVID, but presumably via a different biological mechanism," says Ludwig, who is now working with groups from the Immunosenescence² cluster to clarify whether this hypothesis is correct and, if so, what the effects of this mechanism are on the immune system.

Participating institutions

In addition to the University Hospital Bonn and the University of Bonn, the University Hospital Schleswig-Holstein, the Humanitas University Milan (Italy) and the University Hospital Radboudumc (Netherlands) were also centrally involved.

Promotion:

The study was supported by the NGS Core Facility of the UKB and the BONFOR program of the Faculty of Medicine.

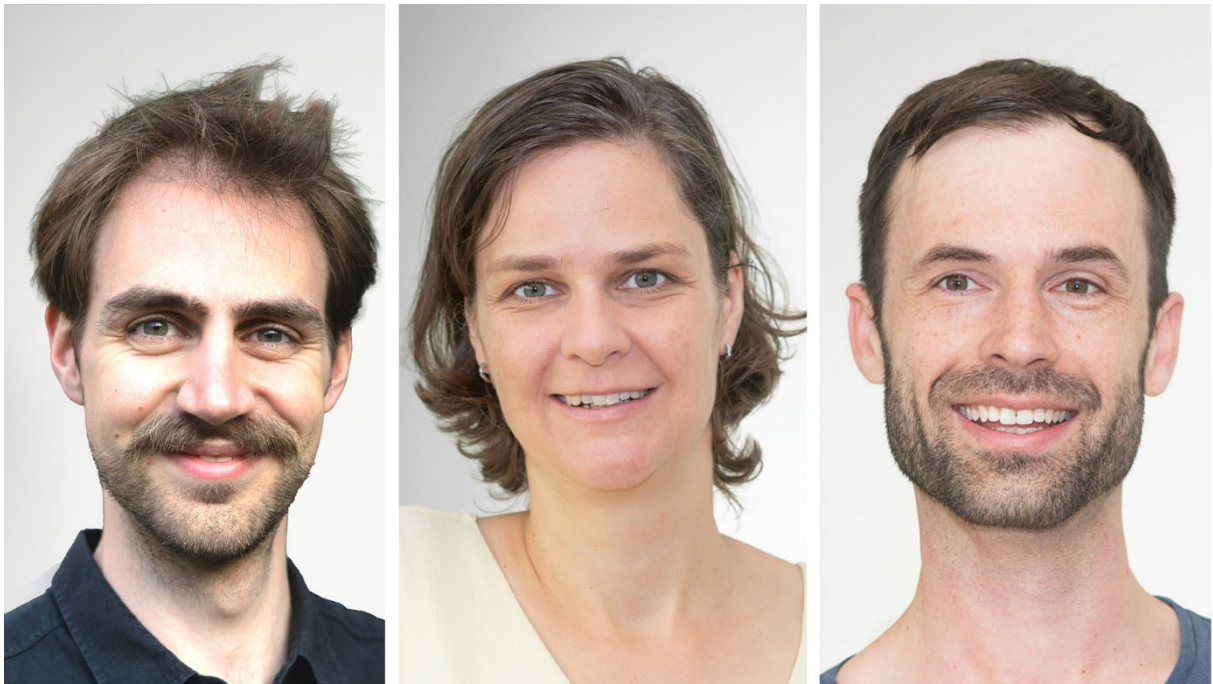
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Image material:



Caption:

Large genetic study on severe COVID-19:

(from left): Jannik Boos, Prof. Kerstin Ludwig und Dr. Axel Schmidt confirm three other genes for increased risk in addition to the known TLR7 gene.

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About Bonn University Hospital: The UKB treats around 500,000 patients per year, employs around 9,500 staff and has total assets of 1.8 billion euros. In addition to the 3,500 medical and dental students, 550 people are trained in numerous healthcare professions each year. The UKB is ranked first among university hospitals in NRW in the Focus Clinic List and has the second-highest case mix index (case severity) in Germany. In 2022 and 2023, the F.A.Z. Institute recognized the UKB as Germany's most desirable employer and training champion among public hospitals in Germany.