

New identification of genetic basis of COVID-19 susceptibility will aid treatment

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This scanning electron microscope image shows SARS-CoV-2 (yellow)—also known as 2019-nCoV, the virus that causes COVID-19—isolated from a patient, emerging from the surface of cells (blue/pink) cultured in the lab. Credit: NIAID-RML

The clinical presentation of COVID-19 varies from patient to patient

and understanding individual genetic susceptibility to the disease is therefore vital to prognosis, prevention, and the development of new treatments. For the first time, Italian scientists have been able to identify the genetic and molecular basis of this susceptibility to infection as well as to the possibility of contracting a more severe form of the disease. The research will be presented to the 53rd annual conference of the European Society of Human Genetics, being held entirely on-line due to the COVID-19 pandemic, today (Saturday).

Professor Alessandra Renieri, Director of the Medical Genetics Unit at the University Hospital of Siena, Italy, will describe her team's GEN-COVID project to collect genomic samples from COVID patients across the whole of Italy in order to try to identify the genetic bases of the high level of clinical variability they showed. Using whole exome sequencing (WES) to study the first data from 130 COVID patients from Siena and other Tuscan institutions, they were able to uncover a number of common susceptibility genes that were linked to a favourable or unfavourable outcome of infection. "We believe that variations in these genes may determine disease progression," says Prof Renieri. "To our knowledge, this is the first report on the results of WES in COVID-19."

Searching for common genes in affected patients against a control group did not give statistically significant results with the exception of a few genes. So the researchers decided to treat each patient as an independent case, following the example of autism spectrum disorder. "In this way we were able to identify for each patient an average of three pathogenic (disease-causing) mutations involved in susceptibility to COVID infection," says Prof Renieri. "This result was not unexpected, since we already knew from studies of twins that COVID-19 has a strong genetic basis."

Although presentation of COVID is different in each individual, this does not rule out the possibility of the same treatment being effective in

many cases. "The model we are proposing includes common genes and our results point to some of them. For example, ACE2 remains one of the major targets. All our COVID patients have an intact ACE2 protein, and the biological pathway involving this gene remains a major focus for drug development," says Prof Renieri. ACE2 is an enzyme attached to the outer surface of several organs, including the lungs, that lowers blood pressure. It serves as an entry point for some coronaviruses, including COVID-19.

These results will have significant implications for health and healthcare policy. Understanding the genetic profile of patients may allow the repurposing of existing medicines for specific therapeutic approaches against COVID-19 as well as speeding the development of new antiviral drugs. Being able to identify patients susceptible to severe pneumonia and their responsiveness to specific drugs will allow rapid public health treatment interventions. And future research will be aided, too, by the development of a COVID Biobank accessible to academic and industry partners.

The researchers will now analyze a further 2000 samples from other Italian regions, specifically from 35 Italian Hospitals belonging to the GEN-COVID project.

"Our data, although preliminary, are promising, and now we plan to validate them in a wider population," says Prof Renieri. "Going beyond our specific results, the outcome of our study underlines the need for a new method to fully assess the basis of one of the more complex genetic traits, with an environmental causation (the virus), but a high rate of heritability. We need to develop new mathematical models using [artificial intelligence](#) in order to be able to understand the complexity of this trait, which is derived from a combination of common and rare genetic factors.

"We have developed this approach in collaboration with the Siena Artificial Intelligence Lab, and now intend to compare it with classical genome-wide association studies³ in the context of the COVID-19 Host Genetics Initiative, which brings together the human genetics community to generate, share, and analyse data to learn the genetic determinants of COVID-19 susceptibility, severity, and outcomes. As a research community, we need to do everything we can to help public health interventions move forward at this time."

Chair of the ESHG conference, Professor Joris Veltman, Dean of the Biosciences Institute at Newcastle University, Newcastle upon Tyne, UK, said: "We are very excited to have this work on the genetics of COVID19 susceptibility presented as one of our late-breaking abstract talks at the ESHG. Our Italian colleagues present the first insight into the role of genetic susceptibility influencing the severity of the response to a COVID19 infection. It needs to be expanded to encompass much larger populations, but it is impressive to see the speed at which research on this virus has proceeded in just a few months' time."

Provided by European Society of Human Genetics

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