Global genomic study could lead to new therapies for COVID patients

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In March 2020, thousands of scientists around the world united to answer a pressing and complex question: which genetic factors influence the wide variation in COVID-19 severity? Why are some patients severely affected while others escape with mild or no symptoms at all?

A comprehensive summary of their findings to date, published in *Nature*—the world's leading multidisciplinary science journal—revealed 13 loci, or locations in the human genome, that are strongly associated with infection or severe COVID-19. The researchers also identified causal factors such as smoking and high body mass index.

The findings could help provide targets for future therapies and illustrate the power of genetic studies in learning more about infectious disease. And these results come from one of the largest genome-wide association studies ever performed, which includes nearly 50,000 COVID-19 patients and two million uninfected controls.

Hamdi Mbarek, Research Partnerships Manager at Qatar Genome Programme (QGP), part of Qatar Foundation's Research, Development and Innovation, and lead analyst of the Qatari dataset, said that scientists from around the world have moved at breakneck speed to unravel the role of genetics in the wide variation in COVID-19 severity—one of the most distinctive and perplexing features of the disease.

He added that the identification of the genetic factors can ultimately lead to potential therapeutic targets in addition to the protection conferred by the vaccines. Both approaches are necessary for improvement in COVID-19 prevention and treatments.

"The more we understand COVID-19 pathogenesis, the better we get at treating and managing the disease. Based on these results, genetic tests are being developed to predict the course of the disease, potential targeted therapies, and drug repurposing candidates are being evaluated," he said.

QGP became the first and only member from the Arab world to contribute to this global effort, called the COVID-19 Host Genomics Initiative. It was founded in March 2020 by Andrea Ganna and Mark

Daly from the Institute for Molecular Medicine Finland, University of Helsinki and the Broad Institute of MIT and Harvard. The initiative has grown to be one of the most extensive collaborations in human genetics and currently includes more than 3,500 authors and 61 studies from 25 countries.

Harnessing diversity

To do their analysis, the consortium pooled clinical and genetic data from the nearly 50,000 patients who tested positive for the virus, and 2 million controls across numerous biobanks, clinical studies, and direct-to-consumer genetic companies such as 23andMe. Because of the large amount of data pouring in from around the world including more than 13,000 genomes from Qatar, the scientists were able to produce statistically robust analyses far more quickly, and from a greater diversity of populations, than any one group could have on its own.

Of the 13 loci identified so far by the team, two had higher frequencies among patients of Asian or Middle Eastern ancestry than in those of European ancestry, underscoring the importance of diversity in genetic datasets. "We've been much more successful than past efforts in sampling genetic diversity because we've made a concerted effort to reach out to populations around the world," said Daly. "I think we still have a long way to go, but we're making very good progress."

The team highlighted one of these two loci near the FOXP4 gene which is linked to lung cancer. The FOXP4 variant associated with severe COVID-19 increases the gene's expression, suggesting that inhibiting the gene could be a potential therapeutic strategy. Other loci associated with severe COVID-19 included DPP9, a gene also involved in lung cancer and pulmonary fibrosis, and TYK2, which is implicated in some autoimmune diseases.

Said Ismail, director of Qatar Genome, says: "We were prepared to join the consortium because we knew how important it is to represent Middle Eastern and Arab genomes in such studies to enhance diversity and empower genetic discoveries and avoid being absent from such key global efforts."

The team hopes their results would point for useful targets for repurposed drugs.

The researchers will continue to study new data as it comes in and update their results through the "Matters Arising" format at *Nature*. They will begin to study what differentiates "long-haulers," or patients whose COVID-19 symptoms persist for months, from others, and continue to identify additional loci associated with infection and severe disease.

"We are keen to harness our data and capabilities to continue contributing to the consortium's several initiatives," says Dr. Asma Al Thani, Chair of Qatar Genome Programme. "We'd like to serve the public interest in light of any developments related to health and prevention for individuals worldwide."

A new space for genetics

Mbarek emphasized that scientists were able to find robust genetic signals because of their collaborative efforts, a cohesive spirit of data-sharing and transparency, and the urgency that comes with knowing that the entire world faces the same threat at the same time.

He added that geneticists, who regularly work in large consortia, have known the benefits of open collaboration for a long time. "This kind of study usually takes three to five years to deliver, by working together we were able to achieve these results in a significantly shorter period of time," Mbarek said.

Qatar has emerged as a leading regional center for genomics research with global impact. It is the only country from its region to contribute to the COVID-19 Host Genetics Initiative study released today in *Nature*, and this first follows other recent milestones. In February 2021, researchers in Qatar released the first and largest comprehensive genome-wide association study of Middle Eastern populations in *Nature Communications*. In May 2021, research from Qatar highlighted in the *New England Journal of Medicine* demonstrating mRNA vaccine efficacy against new COVID-19 variants received wide attention from global media and public health officials.

Ismail, for his part, is excited that results released today in *Nature* are interpretable also in the Qatari population and Arab populations in general. He says QGP will continue to be involved in the large consortia efforts globally in the areas of national disease priorities like common chronic diseases, rare genetic diseases, and cancer.

More information: Mapping the human genetic architecture of COVID-19, *Nature* (2021). DOI: 10.1038/s41586-021-03767-x

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