A Genetic Explanation for Why Some People Had Asymptomatic COVID-19

Jennifer Abbasi

It’s estimated that at least 1 in 5 people with a SARS-CoV-2 infection never develop symptoms. Genetics might explain some of these asymptomatic cases, it turns out. In a new study appearing in *Nature*, people with a particular gene variant appeared to have preexisting T-cell immunity to the virus, likely a holdover from previous bouts of the common cold.

The Backstory
Since the beginning of the COVID-19 pandemic, scientists have investigated the widely varying responses people can have to SARS-CoV-2 infection. It’s now well-known, for example, that advanced age and preexisting health conditions are important risk factors for severe infection. But then why do some healthy young people fall seriously ill with COVID-19 while some older people with comorbidities don’t develop so much as a sniffle?

Jill A. Hollenbach, PhD, MPH, a professor of neurology and of epidemiology and biostatistics at the University of California San Francisco (UCSF), set out to understand the different immunological responses to SARS-CoV-2, particularly asymptomatic cases. Hollenbach’s work at UCSF focuses on variation in the human leukocyte antigen (HLA) system and its effects on human health.

“Because these genes encode molecules that are essential to the immune response to pathogens, asking how this variation impacts disease course in SARS-CoV-2 infection was a natural area of interest for me and many others,” she told *JAMA* in an email.

Why This Is Important
Hollenbach and her coauthors note that many studies have looked at genetic factors in severe COVID-19 disease, but fewer have examined the underpinnings of asymptomatic or mild infection. Insight into factors that allow the immune system to quickly clear the virus could help scientists better understand the disease and improve immunotherapies and vaccines, they say.

The Mechanism
Benjamin Solomon, MD, who was not involved with the work, is clinical director of the National Human Genome Research Institute, part of the US National Institutes of Health. “It’s interesting to see a major study focus on people on the less-affected end of the curve, as this can be clinically important and offer useful biological insights, but may be less studied than the other end of the curve,” Solomon wrote in an email.

The Methods
The researchers recruited nearly 30,000 people into the COVID-19 Citizen Science Study starting in 2020. The participants were potential bone marrow donors in the US whose HLA regions had been sequenced with a high level of detail. They were asked to track their COVID-19 symptoms and outcomes on their smartphones.

The subset of participants analyzed in the current study comprised 1428 unvaccinated White individuals who reported a positive COVID-19 test. The researchers looked for an association between asymptomatic infection and 5 HLA genes in these participants, the “discovery cohort.” They then validated their findings in 2 independent European ancestry cohorts, 1 from the UK and 1 from the US. Finally, they used immunology and structural biology approaches to investigate mechanisms behind the genetic factor they discovered in asymptomatic infections. They did this in part by analyzing T cells collected from the potential bone marrow donors before the pandemic, when they had no possible exposure to the then-novel coronavirus.

What We’ve Learned
In the discovery cohort, 1292 participants had COVID-19 symptoms while 136 participants were asymptomatic. A common variant, or allele, known as HLA-B*15:01 stood out:

- This variant was found in 20% of asymptomatic participants but only 9% of participants who reported symptoms.
- People with 2 copies of the variant, inherited from both parents, were more than 8 times as likely to not have symptoms than those who carried no copies.
- The variant also had a strong association with asymptomatic infection in the 2 independent cohorts.
- A meta-analysis of data from the discovery and independent cohorts found that asymptomatic infections were more than twice as common in people who carried the variant.
- The T cell analysis revealed that before the pandemic even began, participants with the variant had killer T cells that could effectively target SARS-CoV-2.

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a molecular level,” and are recognized by the same T cells, Hollenbach explained.

The researchers concluded in a research briefing that “individuals with HLA-B*15:01 who were previously exposed to seasonal cold viruses might develop immunological memory in the form of T cells that recognize SARS-CoV-2 during a later infection and rapidly kill infected cells.”

The Limitations and Strengths
A key limitation was the lack of diversity in the European ancestry cohorts included in the analysis. The HLA-B*15:01 allele is found in approximately 1 in 10 people with European ancestry but is less common in people with other backgrounds. Hollenbach said her team saw some evidence that the HLA-B*15:01 allele mediates asymptomatic infection in Black individuals who carry it but that they didn’t have the statistical power to say so definitively. The trend toward an association was less clear in Asian and Hispanic people. “At the same time,” she noted, “it is very possible that other alleles are equally or more important in other ancestries. This will be an important area of further investigation for us.”

The self-reported COVID-19 test results and symptoms were another limitation, and could have introduced some margin of error. Solomon said that “ensuring accurate capture of the participants’ COVID-19 symptoms can in general be tricky in these types of studies.” The researchers noted, however, that asymptomatic cases were clinician-defined in the 2 independent cohorts, with similar findings.

A strength of the study, in Solomon’s view, was its use of a combination of methods, including both statistical and functional approaches, to address the underlying question. “Although the COVID-19 pandemic was obviously a catastrophic and horrific event, it is heartening to see how important work continues to be done in an efficient and collaborative way relating to many important basic, translational, and clinical aspects of the disease,” he said.

The Takeaway
The genetic factor uncovered in the study could explain some SARS-CoV-2 infections with no symptoms. “In our cohort this genetic association accounted for about 20% of asymptomatic cases,” Hollenbach said. “So there are likely other genetic and non-genetic factors that are important.”

According to Solomon, the study underscores the fact that there’s not just 1 factor—genetic or otherwise—that can explain COVID-19 outcomes. Susceptibility to COVID-19 “depends on an interplay of factors, including both genetic and nongenetic influences, and these factors may vary from one person to another,” he said. The next steps, he added, “involve translating important findings from this study (and others) to clinical scenarios.”

To that end, Hollenbach said her team thinks the work can inform next-generation vaccines, among other applications. “A first step will be to gain a better understanding of why T cells in these individuals are so incredibly effective at managing the infection.”

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Conflict of Interest Disclosures: Dr Hollenbach reported being associate editor for disease association studies at the journal HLA: Immune Response Genetics and a board member of the journals Human Immunology and International Journal of Immunogenetics and the Society for Immune Polymorphism. Dr Solomon reported being co–editor in chief of the American Journal of Medical Genetics and receiving textbook royalties.

Note: Source references are available through embedded hyperlinks in the article text online.