Genetic Risk of Severe Covid-19

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The large majority of patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have mild or no symptoms,[1] whereas a small proportion of patients have respiratory compromise, acute respiratory distress syndrome, and multiorgan failure (which is often fatal).[2] The determinants of disease severity appear to reside almost exclusively in host factors, not in viral genetic variation.[2]

The article in this issue of the *Journal* about a genomewide association study of severe coronavirus disease 2019 (Covid-19)[3] therefore represents a major leap toward disentangling the molecular mechanisms that cause severe Covid-19. The authors enrolled cohorts of patients at Italian and Spanish epicenters during the local peak of the epidemic, performed genotyping and analyzed data in Norway and Germany, and delivered a complete genomewide association study within approximately 2 months. They enrolled hospitalized patients with confirmed infection who were receiving at least supplemental oxygen therapy and pragmatically compared data from these patients with data from contemporarily recruited blood donors of largely unknown SARS-CoV-2 status and from historical healthy controls from the same regions. They identified associations between the risk of severe Covid-19 and a multigene locus at 3p21.31 and the *ABO* blood group locus at 9q34.2. The carefully scrutinized HLA region did not show any association signal.

Patients with blood group A had an increased risk of severe Covid-19, and those with blood group O had a decreased risk. The strongest signal, however, was the rs11385942 insertion–deletion GA or G variant at locus 3p21.31. The frequency of this GA risk allele was higher among patients who were receiving mechanical ventilation than among those who were receiving supplemental oxygen only, a finding that indicates that this risk allele confers a predisposition to the most severe forms of Covid-19. No such elevated risk-allele frequency among patients receiving mechanical ventilation was observed for the *ABO* locus.

Among the six candidate genes at 3p21.31, *LZTFL1* might be the most compelling, with the rs11385942 variant and all other fine-mapped association signals that exceeded genomewide significance located within it. *LZTFL1* is widely expressed and encodes a protein involved in protein trafficking to primary cilia, which are microtubule-based subcellular organelles acting as antennas for extracellular signals.[4] In T lymphocytes, LZTFL1 participates in the immunologic synapse with antigen-presenting cells,[5] such as dendritic cells (these cells prime T-lymphocyte responses). Of the other five candidate genes, four (*CCR9*, *CXCR6*, *XCR1*, and *FYCO1*) are involved in T-cell and dendritic-cell function, and the fifth (*SLC6A20*) is a transporter with intestinal expression that is regulated by angiotensin-converting enzyme 2 (ACE2), the SARS-CoV-2 receptor.

This genomewide association study will set directions for research. A focus on the immunologic synapse between T cells and antigen-presenting cells appears to be warranted. Severe Covid-19 resembles secondary hemophagocytic lymphohistiocytosis (HLH),[2,6,7] a spectrum of rare, often fatal, hyperinflammatory conditions triggered by autoimmune or autoinflammatory disorders, malignant conditions, and infections (typically by viruses, such as Epstein–Barr virus).[8] Secondary HLH remains poorly understood, but mendelian-inherited primary HLH points toward CD8+ T lymphocytes, natural killer cells, and dendritic cells triggering a cytokine storm involving macrophages.[8] Other shared features between secondary HLH and severe Covid-19 are cytopenia, hyperferritinemia, disseminated intravascular coagulation, acute respiratory distress syndrome, multiple organ dysfunction, excessive expansion of T lymphocytes, and bone marrow histiocytic hyperplasia with hemophagocytosis with aggregates of interstitial CD8+ lymphocytes.[2,6-9]

The markedly lower mortality with dexamethasone treatment added to usual care among patients with Covid-19 who received mechanical ventilation provides strong evidence that death

may be caused by a late hyperinflammatory phase.[10] A therapeutic agent that converts severe Covid-19 into a manageable, nonfatal infection would render the pandemic a lesser concern. Because it is impossible to predict mechanisms straight from genomic coordinates, experimental testing of the biology of implicated genetic risk pathways is a route, albeit a potentially challenging one, toward that goal. After all, cause–effect relationships are a priori resolved by germline associations and randomized, controlled clinical trials.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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DOI: 10.1056/NEJMe2025501