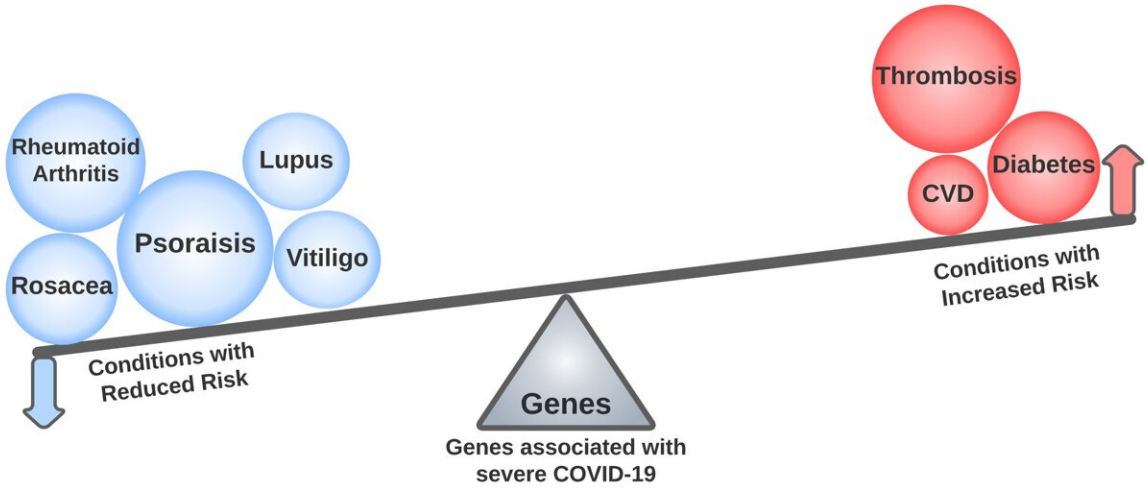
Genetic links revealed between severe COVID-19 and other diseases

April 28 2022



While genes linked to severe COVID-19 were associated with established risk factors and adverse outcomes, including deep vein thrombosis, a significant subset of these genes had opposite associations with reduced risk of immune-mediated disorders such as psoriasis, lupus, and rheumatoid arthritis. Credit: Anurag Verma, Katherine Liao, and Scott Damrauer (CC-BY 4.0, creativecommons.org/licenses/by/4.0/)

A new analysis of data from the Veterans Affairs Million Veteran Program has uncovered genetic links between COVID-19 severity and certain medical conditions that are known risk factors for severe

COVID-19. Anurag Verma of the Corporal Michael Crescenz VA Medical Center in Philadelphia, Pennsylvania, US, and colleagues present these findings on April 28th in the open-access journal *PLOS Genetics*.

Some people with COVID-19 experience the disease more severely than others. Previous research has identified certain variants in specific human genes that are associated with a person experiencing more severe COVID-19. Some of these variants may also be associated with other medical conditions that may already be well understood; identifying these shared variants could improve understanding of COVID-19 and illuminate potential new paths for treatment.

To identify shared variants, Verma and colleagues used an unprecedented dataset of genotypic information linked to electronic health record data (EHR) for more than 650,000 U.S. veterans. They conducted a type of analysis known as a phenome-wide association study (PheWAS) to examine links between variants often found in Veterans who experienced severe COVID-19 and variants associated with a broad selection of medical conditions.

The analysis revealed that certain variants associated with COVID-19 are also associated with known risk factors for COVID-19. Particularly strong links were found for variants associated with venous embolism and thrombosis, as well as type 2 diabetes and ischemic heart disease —two known COVID-19 risk factors.

The analysis also found genetic links between severe COVID-19 and neutropenia for Veterans of African and Hispanic ancestry; these links did not appear for those of European ancestry.

Among respiratory conditions, idiopathic pulmonary fibrosis and chronic alveolar lung disease shared genetic links with severe COVID-19, but

other respiratory infections and chronic obstructive pulmonary disease (COPD) did not. Some variants associated with severe COVID-19 were also associated with reduced risk of autoimmune conditions, such as psoriasis and lupus. These findings highlight the need to carefully weigh various aspects of the immune system when developing new treatments.

Despite some limitations of the PheWAS method, these findings could help deepen understanding of COVID-19 and guide development of new treatments.

Verma concludes, "The study demonstrates the value and impact of large biobanks linking genetic variations with EHR data in public health response to the current and future pandemics. MVP is one of the most diverse cohorts in the US. We had a unique opportunity to scan thousands of conditions documented before the COVID-19 pandemic. We gained insights into the genetic architecture of COVID-19 risk factors and disease complication."

"One thing that stood out to us was the high number of immune-mediated conditions that shared genetic architecture with severe manifestations of COVID-19," coauthor Katherine Liao adds. "The nature of the associations brought to light how the SARS-CoV2 virus pushes on a pressure point in the human immune system and its constant balancing act of fighting infection while maintaining enough control so that it does not also become an autoimmune process, attacking self."

More information: A Phenome-Wide Association Study of genes associated with COVID-19 severity reveals shared genetics with complex diseases in the Million Veteran Program, *PLoS Genetics* (2022). DOI: 10.1371/journal.pgen.1010113