New research suggests a causal link between blood group and severe COVID-19

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A new study has analyzed over 3000 proteins to identify which are causally linked to the development of severe COVID-19. This is the first study to assess such a large number of proteins for their connection to

COVID-19. The findings provide insight into potential new targets for approaches to treat and prevent severe COVID-19.

Published in *PLOS Genetics* and part-funded by the National Institute for Health Research (NIHR) Maudsley Biomedical Research Center, the study used a genetic tool to screen over 3000 proteins. Researchers identified six proteins that could underlie an increased risk of severe COVID-19 and eight that could contribute to protection from severe COVID-19.

One of the proteins (ABO) that was identified as having a causal connection to the risk of developing severe COVID-19 determines blood groups, suggesting that blood groups play an instrumental role in whether people develop severe forms of the disease.

Co-first author Dr. Alish Palmos from Institute of Psychiatry, Psychology & Neuroscience (IoPPN) King's College London said: "We have used a purely genetic approach to investigate a large number of blood proteins and established that a handful have causal links to the development of severe COVID-19. Honing in on this group of proteins is a vital first step in discovering potentially valuable targets for development of new treatments."

Assessing how blood proteins are linked to disease can help understand the underlying mechanisms and identify potential new targets for developing or repurposing drugs. Protein levels can be measured directly from blood samples but conducting this type of research for large numbers of proteins is costly and cannot establish causal direction.

This is where genetics can play a role. Mendelian randomization, a method of comparing causal relations between risk factors and health outcomes, using large genetic datasets can assess the relationship between genetic variants connected with an exposure (in this case high

levels of individual blood proteins) and genetic variants connected with disease outcome (in this case severe COVID-19).

Co-first author Dr. Vincent Millischer from the Medical University of Vienna explained: "Causality between exposure and disease can be established because genetic variants inherited from parent to offspring are randomly assigned at conception similar to how a randomized controlled trial assigns people to groups. In our study the groups are defined by their genetic propensity to different blood protein levels, allowing an assessment of causal direction from high blood protein levels to COVID-19 severity whilst avoiding influence of environmental effects."

The study considered two incremental levels of severity of COVID-19: hospitalization and respiratory support or death. Using data from a number of genome-wide association studies the researchers found six proteins that were causally linked to an increased risk of hospitalization or respiratory support/death due to COVID-19 and eight causally linked to protection against hospitalization or respiratory support/death.

Analysis showed some distinction in types of proteins linked to hospitalization and those linked to respiratory support/death, indicating different mechanisms may be at work in these two stages of disease.

The analysis identified that an enzyme (ABO) that determines blood group was causally associated with both an increased risk of hospitalization and a requirement for respiratory support. This supports previous findings around the association of blood group with higher likelihood of death. Taken together with previous research showing that the proportion of group A is higher in COVID-19 positive individuals, this suggests blood group A is candidate for follow-up studies.

Co-last author Dr. Christopher Hübel from the IoPPN, King's College

London said: "The enzyme helps determine the blood group of an individual and our study has linked it with both risk of hospitalization and the need of respiratory support or death. Our study does not link precise blood group with risk of severe COVID-19 but since previous research has found that proportion of people who are group A is higher in COVID-19 positive individuals, this suggests that blood group A is more likely candidate for follow-up studies."

Researchers also identified three adhesion molecules as being causally linked to a decreased risk of hospitalization and requirement of respiratory support. As these adhesion molecules mediate interaction between immune cells and blood vessels this chimes with previous research suggesting that late stage COVID-19 is also a disease involving the linings of blood vessels.

By identifying this suite of proteins, the research has highlighted a number possible targets for drugs that could be used to help treat severe COVID-19. These will need further clinical investigation which can be undertaken as part of the wider COVID-Clinical Neuroscience Study (COVID-CNS) which is investigating the causes behind different aspects of COVID-19.

Gerome Breen, Professor of Genetics at the IoPPN, and co-last author on the paper said: "What we have done in our study is provide a shortlist for the next stage of research. Out of 1000s of blood proteins we have whittled it down to about 14 that have some form of causal connection to the risk of severe COVID-19 and present a potentially important avenue for further research to better understand the mechanisms behind COVID-19 with an ultimate aim of developing new treatments but potentially also preventative therapies."

The paper "Proteome-wide Mendelian randomization identifies causal links between blood proteins and severe COVID-19" was published in

PLOS Genetics.

More information: Proteome-wide Mendelian randomization identifies causal links between blood proteins and severe COVID-19, *PLOS Genetics* (2022). DOI: 10.1371/journal.pgen.1010042

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