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Host Proteins Engaged with SARS-CoV-2 Contamination

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Opinion

SARS-CoV-2 is the seventh coronavirus known to infect humans; SARS-CoV, MERS-CoV, and SARS-CoV-2 can cause severe disease, whereas HKU1, NL63, OC43, and 229E are associated with mild symptoms. In this section, we look at what we can learn about the origins of SARS-CoV-2 by comparing genomic data. We provide a perspective on the notable features of the SARS-CoV-2 genome and discuss the scenarios that could have resulted in their emergence. Our findings demonstrate unequivocally that SARS-CoV-2 is not a laboratory construct or a virus that has been purposefully manipulated.

The pandemic of SARS-CoV-2 infection, the cause of COVID-19, is causing severe global disruption and excess mortality. While vaccine-derived population immunity is ultimately required, in the short term, there is a need to develop new therapies or repurpose existing drugs that are effective in treating patients with severe COVID-19 complications, as well as to identify agents that may protect vulnerable individuals from becoming infected.

The experimental characterization of 332 SARS-CoV-2-human protein–protein interactions and their mapping to 69 existing FDA-approved drugs, drugs in clinical trials, and/or preclinical compounds points to new therapeutic strategies, some of which are currently under investigation. The measurement of circulating host proteins associated with COVID-19 severity or mortality provides insight into potentially targetable maladaptive host responses, with current focus on the innate immune response, coagulation and novel candidate proteins.

Natural sequence variation in or near a human gene encoding a drug target and affecting its expression or activity can provide direct support for drug mechanisms and safety in humans. This approach is now used by major pharmaceutical companies to identify and validate drug targets for a wide range of noncommunicable diseases, as well as to guide drug repurposing. The genetic evidence linking molecular targets to diseases is based on our understanding of drug target genetic architecture. Proteins are the most common biological class of drug targets, and advances in high-throughput proteomic technologies have enabled systematic analysis of the "human druggable proteome" and genetic target validation to rapidly accelerate therapeutic target prioritisation (or de-prioritization) for new drug development or repurposing trials.

The identification and detailed genetic characterization of proteins used by SARS-CoV-2 for entry and replication, as well as those involved in the maladaptive host response, will aid in understanding the systemic consequences of COVID-19. If confirmed, the reported protective effect of blood group O on COVID-19-induced respiratory failure could be mediated by the effect of genetically reduced activity of a ubiquitously expressed glycosyltransferase on a variety of proteins.

We used large-scale genomic and aptamer-based plasma proteomic data from a population-based study of 10,708 people prior to any SARS-CoV-2 infection or COVID-19 infection to characterise the genetic architecture of 179 host proteins relevant to COVID-19. We discovered genetic variants that control host proteins that interact with SARS-CoV-2 or that may contribute to the maladaptive host response. We thoroughly characterise protein quantitative trait loci (pQTLs) in close proximity to protein-encoding genes (500 kb window around the gene body), cis-pQTLs, and use genetic score analysis and phenome-wide scans to investigate the potential consequences of drug targeting of those proteins. Our findings support the use of genetic variants as drug target validation tools in emerging genome-wide association studies (GWAS) of SARS-CoV-2 infection and COVID-19.

Host factors related to candidate proteins

For 63 of 106 aptamers, genetic factors explained more variance than any other tested host factor, with IL-6 sRa, collagen a1 (VI), or QSOX2 being the most powerful genetically determined examples. The composition of non-genetic host factors responsible for the majority of the explained variance appeared to be protein-specific. For SMOC1 and Interleukin-1 receptor-like 1, for example, sex explained 23.8 percent and 17.9 percent of the variance, indicating that men and women have different distributions.

Plasma alanine aminotransferase (15.4 percent of the variance of NADPH-P450 oxidoreductase) and age (14.2 percent of the variance of GDF-15/MIC-1) are two other examples of single factors with significant contributions. For proteins such as LG3BP, SAA, IL-1Ra, or HO-1, we observed a strong and diverse contribution from different non-genetic factors, implying multiple, in part modifiable, factors with independent contributions to plasma levels of those proteins.

Patients with multiple chronic conditions are more likely to develop severe COVID-19 disease, so we looked at the impact of disease susceptibility on protein targets of interest using genetic risk scores (GRS) for major metabolic (e.g., type 2 diabetes, BMI, and waist-to-hip ratio (WHR)), respiratory (e.g., asthma), and cardiovascular (e.g., coronary artery disease (CAD)) phenotypes.

The successful identification of candidate druggable targets for COVID-19 provides information on both potential therapies and medications that may worsen the outlook, depending on the genetic effect and whether any associated compound inhibits or activates the target. We also discovered genetic evidence that certain protein targets, such as MARK3 and monocyte count, have the potential to have negative effects on other health outcomes, but this was not a general feature of all tested "druggable" targets. Furthermore, detailed characterization of the identified targets will be required as a first step in determining the likelihood of success of any new or repurposed drugs identified.

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