Rapid Reviews COVID-19

Review 1: "Genetic association analysis of SARS-CoV-2 infection in 455,838 UK Biobank participants"

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Published on: Dec 09, 2020

RR:C19 Evidence Scale rating by reviewer:

- **Reliable.** The main study claims are generally justified by its methods and data. The results and conclusions are likely to be similar to the hypothetical ideal study. There are some minor caveats or limitations, but they would/do not change the major claims of the study. The study provides sufficient strength of evidence on its own that its main claims should be considered actionable, with some room for future revision.

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Review:

The authors use genetic data from UK Biobank participants to determine whether certain loci are associated with COVID19 susceptibility or severity upon contraction of the disease. In the course of their study, they attempt to reproduce the findings of prior studies as well as look for associations between their phenotypes and potentially informative or novel sites. The analyses performed appear rigorous to me, though I have some concerns about potential biases in the sample of infected individuals as well as insufficient sample sizes. That said, these challenges are functionally impossible to fully confront in the context of the ongoing pandemic, and the authors do discuss them in the text and account for other phenotypes in certain situations (e.g., Alzheimer's).

Overall, I think the analyses presented are informative, providing helpful support and context to previous studies which are also likely to suffer from potential difficulties in sample collection. In particular, confirmation (or the lack thereof) of loci which may be associated with population structure is critical to avoid spending resources improperly and to better understand how to treat diverse populations. This study makes headway in these directions, including, for instance, the analysis of the ABO locus. I found the authors' interpretation of their findings to be grounded and aware of potential limitations. Though few loci were identified, I feel the attempts at replication and investigation of loci with clinical significance is important to the community as additional studies are released. The exposition is lucid and the results dashboard a helpful addition to improve accessibility to the reader.

In light of the rapid developments in this area of research, I think the manuscript can be accepted in its current state, though I would be interested to see follow ups with additional infected patients or loci identified by other groups for a more formal review process.