Review 1: "Unusual Features of the SARS-CoV-2 Genome Suggesting Sophisticated Laboratory Modification Rather Than Natural Evolution and Delineation of Its Probable Synthetic Route"

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RR:C19 Evidence Scale rating by reviewer:

- **Misleading.** Serious flaws and errors in the methods and data render the study conclusions misinformative. The results and conclusions of the ideal study are at least as likely to conclude the opposite of its results and conclusions than agree. Decision-makers should not consider this evidence in any decision.

Review:

COVID-19 caused by SARS-CoV-2 has damaged economies of nations in unprecedented degree and the virus has exposed the fragilities and vulnerabilities of our society against novel pathogens. Therefore, the origin of the virus needs to be identified promptly and unambiguously to prevent further damages and future occurrences of similar pandemics. Unfortunately, as of today, we have not identified viable intermediate host candidates for SARS-CoV-2, yet. In this manuscript "Unusual Features of the SARS-CoV-2 Genome Suggesting Sophisticated Laboratory Modification Rather Than Natural Evolution and Delineation of Its Probable Synthetic Route", authors have implied that SARS-CoV-2 is engineered rather than naturally emerged. Such possibility should not be ruled out if compelling scientific evidences are exhibited.

The authors claim that SARS-CoV-2 was engineered from CoV ZC45, which was obtained from a bat sample captured in Zhoushan in 2017[1]. A variant analysis with respect to SARS-CoV-2 is performed and over 3000 genomic differences are identified between ZC45 and SARS-CoV-2 genomes. Authors need to explain how these differences are engineered in a similar manner to their argument in spike protein with specific restriction enzymes utilized. In practical point of view, ZC45 cannot be a template and authors need to find a better template.

Furthermore, authors' speculation of furin cleavage insert PRRA in spike protein seemed quite interesting at first. Nevertheless, recently reported RmYN02 (EPI_ISL_412977), from a bat sample in Yunnan Province in 2019, has PAA insert at the same site[2]. While the authors state that RmYN02 is likely fraudulent, there are no concrete evidences to support the claim in the manuscript. In addition, argument of codon usage of arginine in PRRA is not convincing since these are likely derived from some kind of mobile elements in hosts or other pathogens. Further investigations are necessary to unravel the mystery of the PRRA insert.

For these reasons, we conclude that the manuscript does not demonstrate sufficient scientific evidences to support genetic manipulation origin of SARS-CoV-2.

References

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