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Letter to the Editor

Could nucleocapsid be a next-generation COVID-19 vaccine candidate?

We have read with interest the article by Oronsky *et al.* (2022) about including the SARS-CoV-2 nucleocapsid (N) protein in future COVID-19 vaccines. One of the main reasons for this suggestion is that the N gene is much less vulnerable to mutation and may provide stronger immunity to novel viral variants. Although when the proteins of SARS-CoV-2 and SARS-CoV are compared, the N protein is more conserved than the spike (S) protein (Dutta *et al.*, 2020); the current data we have analyzed about SARS-CoV-2 mutations show that the N gene is one of the most mutated genes (Figure 1). From the Global Initiative on Sharing Avian Influenza Data (GISAID) database, we collected 5,340,569 high-coverage SARS-CoV-2 genomes, available until June 27, 2022, and compared them with the reference SARS-CoV-2 genome (NC_045512.2) isolated in December 2019 from Wuhan-Hu-1. All the mutations were collected. For the N gene, 2551 nonsynonymous and 839 synonymous mutations were found. Because the length of the N gene is 1260 nucleotides, these values represent, respectively, 202.5 and 66.6 unique mutations per 100 nucleotides. As is shown in Figure 1, after the open reading frames that encode accessory proteins and the gene that encodes the leader peptide (nsp1), the N gene displays more nonsynonymous mutations and deletions than most of the SARS-CoV-2 genes, including the S gene. The genes with fewer nonsynonymous mutations are the helicase (nsp13), nsp10, nsp9, M-pro (nsp5), and RNA polymerase (nsp12) (Figure 1). Synonymous mutations are more uniform in SARS-CoV-2 genes, with between 55.6 and 71 mutations per 100 nucleotides. Insertions, on the other hand, are much less frequent.

The high mutation frequency of the N gene does not mean that it cannot be used to create future COVID-19 vaccines. Mutations in the N gene are not uniformly distributed (Zhao *et al.*, 2022). One of the most conserved regions is found in the central disordered linker proximal to the N-G215C mutation (Zhao *et al.*, 2022). Thus, this conserved region could be of use to create the vaccines.

Declaration of competing interest

The authors have no competing interests to declare.

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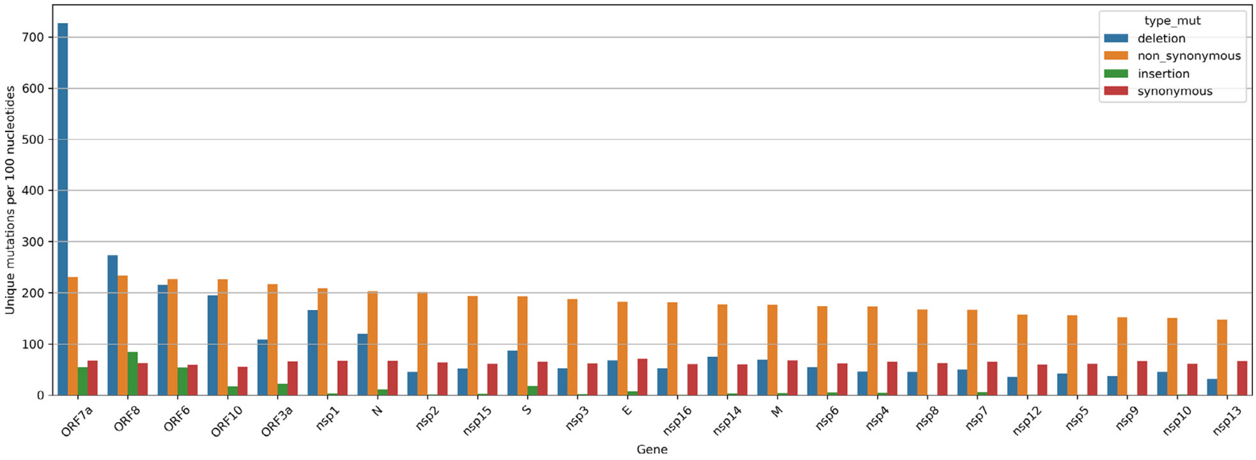

Figure 1. Unique mutations per 100 nucleotides in the SARS-CoV-2 genes. Deletions, nonsynonymous mutations, insertions, and synonymous mutations are shown in blue, yellow, green, and red, respectively. 5,340,569 high-coverage SARS-CoV-2 genomes, available at GISAID until 27 June 2022, were analyzed, and 84,176 mutations, 22,090 deletions, and 2328 insertions were obtained.

Abbreviations: GISAID, Global Initiative on Sharing Avian Influenza Data.
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Author contributions

BS-E curated and analyzed the data and wrote the manuscript. SG-V conceptualized the study, organized the workflow, contributed to data curation, analyzed the data and contributed to the writing of the manuscript. GP analyzed the data and critically read the manuscript. GM helped with figure 1. All authors have read and agreed to the published version of the manuscript.

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