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LETTER TO THE EDITOR

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Mutational and phylogenetic analyses of the two lineages of the Omicron variant

Dear Editor,

Based on the recommendation of the WHO's Technical Advisory Group on Virus Evolution, WHO designated the variant B.1.1.529 as a variant of concern (VOC) and named Omicron on 26 November, 2021. Omicron was first observed in Africa in mid-November 2021.[1] The infection by this variant has been rapidly spreading and 85 countries have already reported the cases of human infection with this variant as of 15 December 2021.[2] The rapid spread of Omicron has again fueled the fears of COVID-19 all around the world like other four VOCs (Alpha, Beta, Gamma, and Delta).

Recently, the Omicron variant has classified into two different lineages BA.1 and BA.2 based on the mutations, some of which are common and some are unique to both lineages.[3,4] Still, there is no clear evidence or published article on the mutational diversity and phylogenetic analysis of these two lineages. Therefore, in the present study, we have performed the whole-genome mutational mapping and phylogenetic analysis of BA.1 and BA.2 lineages. We have downloaded 6 genome sequences each of BA.1 and BA.2, and also the genome sequence of the prototype strain (hCoV-19/Wuhan/WIV04/2019) from the Global Initiative on Sharing All Influenza Data (GISAID) and performed whole-genome mutational analysis according to the protocol described in Sarkar et al.[5,6] Each of the six genomes of both BA.1 and BA.2 lineages was found to have 51 mutations dispersed throughout the genome, 32 of which are common to both lineages, whereas each lineage has 19 signature mutations. Among 32 common mutations, 21 are present in the S glycoprotein and the rest 11 are present in the other four coding regions (ORF1ab, E, M, and N). Nineteen unique mutations of BA.1 include 13 in the S glycoprotein and that of BA.2 includes 7 in the S glycoprotein (Table 1). Phylogenetic analysis of 12 genome sequences of Omicron variant, encompassing 6 genomes each of BA.1 and BA.2, along with the 2000 genomes of 25 different clades by Ultrafast Sample placement of Existing tRees,[6,7] revealed that

TABLE 1 List of common and unique mutations present within the genome of BA.1 and BA.2 lineages

Common mutations of BA.1 and BA.2 lineages (n = 32)	Unique mutations of BA.1 lineage (n = 19)	Unique mutations of BA.2 lineage (n = 19)
ORF1ab: T3255I, P3395H, SGF3675del, P4715L, I5967V	*ORF1ab*: K856R, SL2083I, A2710T, L3674F, I3758V	*ORF1ab*: S135R, T842I, G1307S, L3027F, T3090I, L3201F, F3677L, R5716C, T6564I
S glycoprotein: G142D, G339D, S373P, S375F, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K	*S glycoprotein*: A67V, HV69del, T95I, VYY143del, N211del, L212I, 215EPEins, S371L, G446S, G496S, T547K, N856K, L981F	*S glycoprotein*: T19I, LPPA24S, V213G, S371F, T376A, D405N, R408S
		ORF3a: T223I
E: T9I		
M: Q19E, A63T	*M*: D3G	
		ORF6: D61L
N: P13L, ERS31del, RG203KR		*N*: S413R

Note: Red color indicates the mutations of the receptor-binding domain (RBD) of S glycoprotein. Violet color indicates the mutation of the N-terminal domain (NTD) of S glycoprotein.

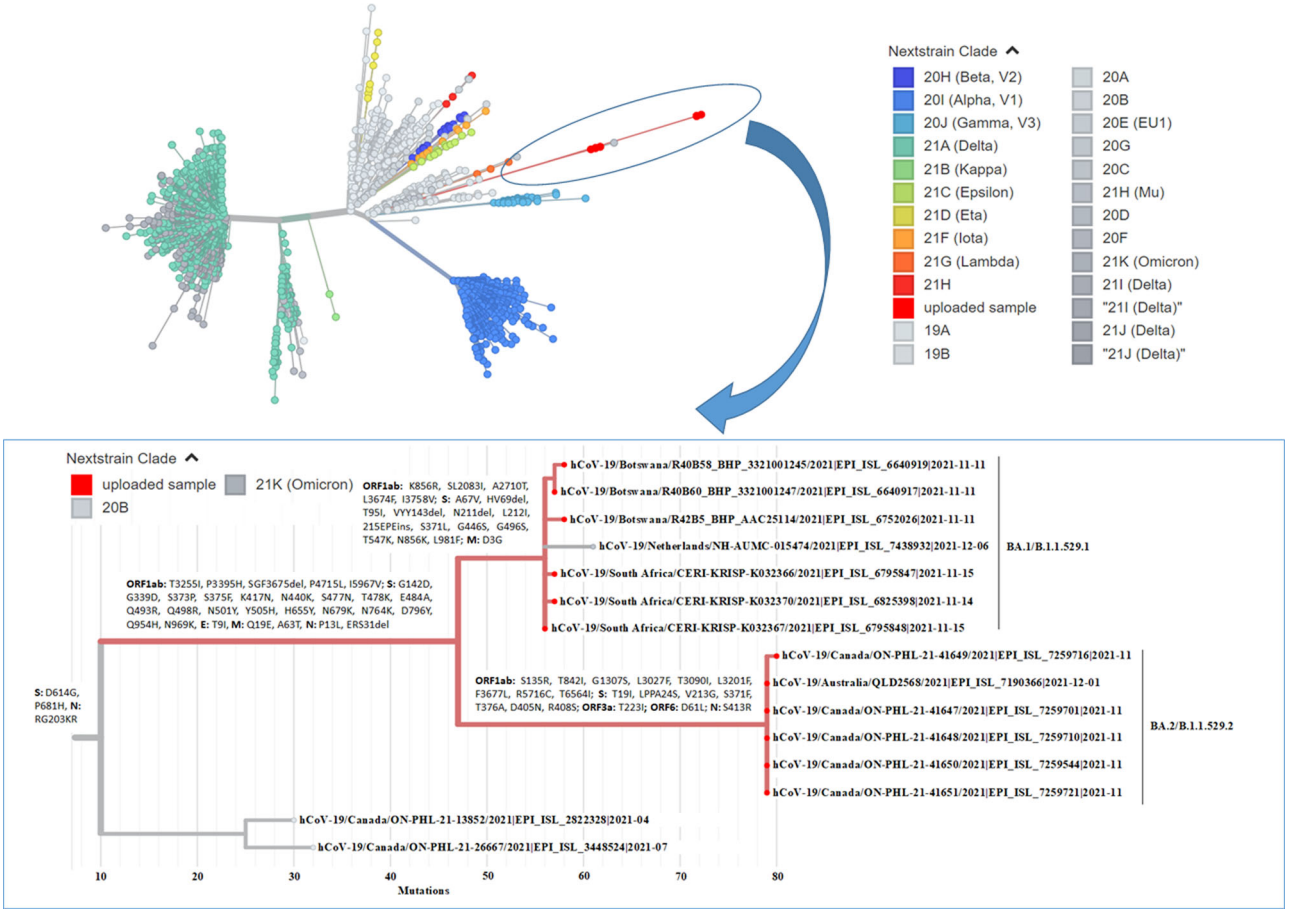

FIGURE 1 Phylogenetic analysis of the Omicron variant by Ultrafast Sample placement of Existing tRee (UShER). The phylogenetic tree (unrooted tree) was constructed with a total of 2012 SARS-CoV-2 strains involving 12 strains of the Omicron variant (red color) and 2000 strains from 25 different clades. Each color in the tree is representing a different clade/lineage

genomes of Omicron variant formed a new cluster that emerged from the 20B clade (also known as GR) and also subdivided into two different subclusters (BA.1 and BA.2) based on the unique mutations (Figure 1).

The S glycoprotein mediates virus attachment to ACE2 receptor, membrane fusion, and entry into the host cell, and also acts as a primary target for neutralizing antibodies elicited by the host immune response.[8] Presence of 34 and 28 mutations in the S glycoprotein of BA.1 and BA.2, respectively, raising concern whether these lineages have increased transmissibility, immune escape potential, and virulence compared to other circulating SARS-CoV-2 strains especially Delta which is currently dominating worldwide. Seven mutations of both BA.1 and BA.2 (G142D, K417N, T478K, N501Y, D614G, H655Y, and P681H) and three mutations of BA.1 (ΔHV69del, T95I, and ΔYY144del) overlap four other VOCs (Alpha, Beta, Gamma, and Delta) and have previously been linked with high transmissibility, increased viral binding affinity, and immune evasion.[9–12] Functional implication of the remaining mutations of the S glycoprotein and other coding regions of BA.1 and BA.2 still unknown, leaving a question of how the whole set of mutations of the two lineages will affect viral fitness.

Preliminary evidence indicated that Omicron has increased infectivity and a high transmission rate compared to Delta.[13–15] However, whether the rapid spread of Omicron in countries with increased population immunity is due to increased transmissibility and/or immune evasion remains unclear. Though, some recent studies have claimed the immune evasion properties of the Omicron.[14–17] Based on this existing evidence, Omicron is anticipated to overtake Delta in areas where community transmission occurs. The severity of Omicron infection still remains elusive. Preliminary studies from South Africa suggested that Omicron may be less severe than Delta,[18] and all COVID-19 patients, infected with Omicron, from countries of EU and EEA either showed mild symptoms or were asymptomatic.[19] Detection accuracy of routinely used PCR and antigen-based rapid diagnostic test (Ag-RDT) assays was not found to be influenced by most of the Omicron strains. However, the BA.1 lineage showed S gene target failure (SGTF) in RT-PCR assay due to multiple deletions in the NTD of S glycoprotein, whereas BA.2 lineage may skip SGTF due to lack of deletions in the NTD. Overall, the global threat related to Omicron remains very high for its potential to escape humoral immune response and high transmissibility, which may lead to another wave of COVID-19 with severe consequences.[19]

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Swagata Majumdar and Rakesh Sarkar conceived the study. Swagata Majumdar performed sequence retrieval of SARS-CoV-2 and whole-genome mutational analysis. Rakesh Sarkar performed the phylogenetic analysis and drafted the manuscript. All authors revised the manuscript and approved the final manuscript for submission.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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