Mutational Profile of SARS-CoV-2 Spike Protein in Brazilian isolates

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Short Report

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Abstract

Due to the essential role of S protein in early steps of SARS-CoV-2 replication, high antigenicity and surface exposure the spike protein has been recognized as the most promising molecular target for neutralizing antibodies, diagnostic methods, vaccines, and antiviral drugs development to control the COVID-19. In this study we analyzed the most predominant mutations in S protein of Brazilian isolates and predicted the effect of these amino acids alterations to protein conformation. A total of 2869 sequences were obtained from GISAID for five regions of Brazilian territory (Midwest, North, Northeast, South and Southeast) according to exclusion criteria. Prediction effects of the amino acids substitutions on the structure dynamics of spike protein indicated a positive ΔΔG value for seven mutations and negative for three mutations. These seven mutations also had positive values of ΔΔSVib which is associated to reduction of molecular flexibility of spike protein allowing for adaptative convergent evolution principles to take place. These lineages which are circulating in Brazil, which based on structure-based prediction of protein stability, maybe are changing in different conformational states affecting infectivity and our results point to an increased stability and reduced flexibility of the P1 variant of concern. The advance of infections and re-infections require continuous genomic surveillance studies in order to characterize emerging mutations and monitoring of vaccines efficacy thus considering structural data and dynamics in the observed phenotypes.

Introduction

Coronaviruses (CoVs) consists of a wide group of enveloped viruses from *Coronaviridae* family which transmit respiratory, enteric, liver and neurological diseases in several avian and mammalian species (Woo et al., 2009). Human coronaviruses (hCoVs) infections were associated to mild diseases until the global emergence of Middle East respiratory syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV) coronaviruses in 2002 and 2012, respectively (Drosten et al., 2003; Nassar et al., 2018; Peret et al., 2003; Zaki et al., 2012). In late December 2019, several cases of pneumonia of unknown origin were reported in Wuhan (China) and in January 2020 the causal agent was defined as the severe acute respiratory syndrome (SARS-CoV 2) (Wu et al., 2020). SARS-CoV-2 infections spread rapidly worldwide, and the World Health Organization declared a pandemic status for the disease caused by SARS-CoV-2 infection (COVID-19) which currently has more than 130 million confirmed cases with global distribution (WHO, 2021).

SARS-CoV-2 genome is a (+) ssRNA of approximately 30 kb which encodes for nonstructural proteins (NSPs) from two open reading frames 1a and 1b (ORF1a and ORF1b) that is cleaved into individual nonstructural proteins (NSPs). Subgenomic RNAs (sgRNAs) are synthesized from negative-sense RNA intermediates and subsequently sgRNA is translated into four structural proteins such as spike (S), envelope (E), membrane (M) and nucleocapside (N) (Dongwan et al., 2020). In addition, six accessories proteins are encoded by ORF3a, ORF6, ORF7a, ORF7b, and ORF8 genes (Khailany et al., 2020; Li et al., 2005; Oostra et al., 2007).

The Spike (S) protein is a conserved, transmembrane class I fusion, glycoprotein that mediates CoVs entry into host cells (Du et al., 2009; Lan et al., 2020). This protein forms homotrimers in the mature viral surface and comprises two functional subunits denominated S1 and S2, which are responsible for binding into cell receptor such as angiotensin-converting enzyme 2 (ACE-2) and for fusion of viral and cellular membranes, respectively (Walls et al., 2020). Due to the essential role of S protein in early steps of viral replication, high antigenicity and surface exposure the spike protein has been recognized as the most promising molecular target for neutralizing antibodies, diagnostic methods, vaccines, and antiviral drugs development (Moura et al., 2021; Suryadevara et al., 2021; Townsend et al., 2021).

Studies on the evolutionary dynamics of structural proteins of SARS-CoV-2 are useful for development of novel vaccines, diagnostic tests and therapeutic strategies. It has been observed that several amino acids substitutions in the S protein had affected virulence properties worldwide. In this study we analyzed the most predominant mutations in S protein of Brazilian isolates and predicted the effect of these amino acids alterations to protein conformation.

Results

A total of 2869 sequences were obtained from GISAID for five regions of Brazilian territory (Midwest, North, Northeast, South and Southeast) according to exclusion criteria. Southeast region showed the highest number of RNA sequences available on GISAID (1122; 39.1%), followed by North (644; 22.4 %), Northeast (533; 18.62%), South (436; 15.2%), and Midwest (134; 4.7%). The states of Sao Paulo (SP), Rio de Janeiro (RJ) and Rio Grande do Sul (RS) had the highest number of sequences (533, 485 and 324, respectively). In addition, at least one mutation was detected in 94.9% of genomes (2722 of 2869).

The SARS-CoV-2 genome sequences from Brazil revealed the most prevalent variants belongs to the clade GR (2457/2722; 90.3%), G (119/2722; 4.4%) and GH (23/2722; 0.8%). The G clade genomes, including GH and GR sub-clusters, are predominant in Europe specially United Kingdom, Portugal and Russia (Mercatelli and Giorgi, 2020; Resende et al., 2020). The L genome, which is related to the SARS-CoV-2 reference genome, were only detect in two genomes sample from The State of Bahia.

Amino-acid mutation frequency of spike proteins were analyzed, and the top ten sequences are described in Table 1. A total of 208 amino acid positions substitutions found in the S protein sequences. The subunits S1 and S2 presented with 114 and 85 substitutions, respectively. Most of these amino acid substitutions were D614G, V1176F and E484K. Among the deletions an overall 139 mutations were detected in nine amino acids: Y144 (50/139), H69(40/139), V70 (36/139), V143(4/139), G142 (4/139), L141(3/139), R190 (1/139) and L189 (1/139).

Prediction of effect of the amino acids substitutions on the structure dynamics of spike protein indicated a positive ΔΔG value for seven mutations and negative for three mutations, as described in Table 2. The most prevalent mutations in Brazil (D614G, V1176F and E484K) and H655Y showed higher ΔΔG value indicating a great stabilizing effect on structural dynamics of the S protein. These seven mutations also had positive values of ΔΔSVib which is associated to reduction of molecular flexibility of spike protein.

Discussion

The rapid spread of SARS-CoV-2 worldwide has been associated to a large number of genomic mutations leading the emergence of new lineages. Currently, Brazil reported more than 12 million of SARS-CoV-2 infections and have been considerate the epicenter of COVID-19 pandemic. Thus, the investigation of the mutational spectra of Brazilian isolates of SARS-CoV-2 are important tools comprehension of virulence, drugs and vaccines efficacy of emerging lineages.

The subunit S1 of the S protein (14–685 residues) plays an essential role in the transmission and pathogenesis of COVID-19 involving the binding of the virus to the host cellular angiotensin-converting enzyme (ACE-2) in host cell-surface. In this study, we found a high number of amino acid substitution in S1 in comparison to S2 subunit (114 versus 85). The D614G mutation occurs in SD2 domain of S1 subunit and have been classified under the G clade. Since the emergence of COVID-19 pandemic several studies have reported the critical role of D614G in the increase of infectivity, transmissibility, and mortality rate of SARS-CoV-2 worldwide (Mahmoudi Gomari et al., 2021; Mohammad et al., 2021; Plante et al., 2020). In addition, the global prevalent mutation D614G is related to immune system evasion process. Our data indicated D614G is the dominant form among Brazilian isolates containing at least one mutation (2645/2722; 97%).

The V1176F was found in 52% of the SARS-CoV-2 isolated sequences evaluated herein. As opposed to D614G, the V1176F mutation occurs in the subunit S2 of S protein (686–1273 residues) which mediates fusion of viral and host cell membranes leading to the release of SARS-CoV-2 genome into host cell. Despite no antigenic effect has yet been reported to V1176F, this variation along with D614G have been positively correlated to increased severity and mortality rates in Saudi-Arabia and South America, including Brazil (Farkas et al., 2020).

Up to this point, the variants of concern with most spread of the SARS-CoV-2 worldwide originated in United Kingdom (B.1.1.7), South Africa (B.1.351) and Brazil (P.1 and P.2). These lineages were strongly associated to an increase in transmissibility, mortality and re-infections reports due to the high incidence of E484K, N501Y and K417N mutations in the in RDB domain of S1 subunit of S protein. In this study, we found that mutations E484K, N501Y and K417N have high frequency among Brazilian isolates. According to our data, recent structural studies have described the role of emerging variants containing E484K, N501Y and K417N mutations on alteration of molecular flexibility of S protein mediating the increase the affinity of RBD to ACE2 receptor and facilitating SARS-CoV-2 infection (Khan et al., 2021; Ortuso et al., 2021). The effect of E484K, N501Y and K417N mutations variants in the reduction of neutralizing activity of human convalescent and post-vaccination sera remains unclear (Jangra et al., 2021; Xie et al., 2021).

These events suggest that emerging mutations are associated with independent founding events evaluating to a convergent adaptative evolution of the virus in naive populations, our results are in

agreement with stabilizing mutation studies which suggest more rigid structural bodies in natural selection. Hydrogen bonds (H-bonds) and hydrophobic interactions are important specific interactions in the maintenance and stabilization of tridimensional structure of proteins. The increased number of H-bonds (e.g. mutant E484 establish interactions to E488 and E490 residues) and hydrophobic (e.g. mutant F1176 establish interactions to C956 and C957 residues) interactions observed in our experiments are suggestive of more rigid structures and our ΔΔG results are also in agreement with this statement (Figure 1). Actually, more than 12 million positive confirmed cases of SARS-CoV-2 infections in Brazil. There is a lack in genomic monitoring of SARS-CoV-2 in Brazil. Thus, the advance of infections and re-infections require continuous genomic surveillance studies in order to characterize emerging mutations and monitoring of vaccines efficacy.

Materials And Methods

In order to evaluated genetic variations of the S protein, we retrieved 3,093 genome sequences of SARS-CoV-2 isolated in Brazil available at *Global Initiative On Sharing All Influenza Data* (GISAID - https://www.gisaid.org) up to March 25, 2021. These sequences belong to infected patients from 26 states in Brazil and 1 Federal District. The search was refined by exclusion of low quality, ambiguous and non-human host RNA sequences through search filters available in GISAID platform. Sequence alignment and amino-acid mutation frequency analysis of S glycoprotein was performed using *CoVSurver mutations app* (https://www.gisaid.org/epiflu-applications/covsurver-mutations-app/). The complete genome sequence of SARS-CoV-2 hCoV-19/Wuhan/WIV04/2019 was used as a reference.

Single mutational effect on tertiary structure, molecular stability, and flexibility of S protein were predicted by DynaMut server (Rodrigues et al., 2018). Simulations were carried out using the three-dimensional model of SARS-CoV-2 S (PDB 7CWU) selected from Protein Data Bank (PDB). Dynamut server calculated the difference of free energy (ΔΔG) and change in vibrational entropy energy (ΔΔSVib) between wild-type and mutant proteins.

Declarations

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Author’s contributions

F.R.S.S., C.R.P., project design. M.S.P.A., M.B., H.H.M.C., D.G.R., G.G., G.M.P.M., B.P.C., handle and management biologicals data. F.R.S.S., D.F.L.N., C.R.P., data, and statistical analysis. F.R.S.S., and C.R.P. wrote the manuscript. All authors (F.R.S.S., S.P.A., M.B., H.H.M.C., D.G.R., G.G., G.M.P.M., B.P.C., D.F.L.N., C.R.P.,) reviewed and edited the manuscript.

Additional Information

Dataset of genomes isolates are available in supplemental material

Competing interests

The authors declare no competing interest within the scope of this manuscript.

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Tables

Table 1. Rank of major mutations and the effect on the structural dynamics of spike protein.

Rank	Mutation	Frequency	ΔΔG DynaMut[a]	Outcome	$\Delta\Delta S_{Vib}$ ENCoM[a]	Flexibility
1	D614G	2645	1.541	Stabilizing	-0.397	Decrease
2	V1176F	1411	0.730	Stabilizing	-0.080	Decrease
3	E484K	894	1.215	Stabilizing	-1.066	Decrease
4	N501Y	348	-0.325	Destabilizing	4.129	Increase
5	D138Y	310	1.142	Stabilizing	-1.293	Decrease
6	H655Y	309	1.850	Stabilizing	-0.611	Decrease
7	P26S	307	0.392	Stabilizing	-0.602	Decrease
8	L18F	306	-0.575	Destabilizing	0.168	Increase
9	T1027I	306	0.847	Stabilizing	-0.363	Decrease
10	K417T	304	-0.080	Destabilizing	0.047	Increase

[a]The ΔΔG and ΔΔSVib ENCoM values are expressed in kcal.mol^{-1} and kcal.mol^{-1}.K^{-1}, respectively.

Figures

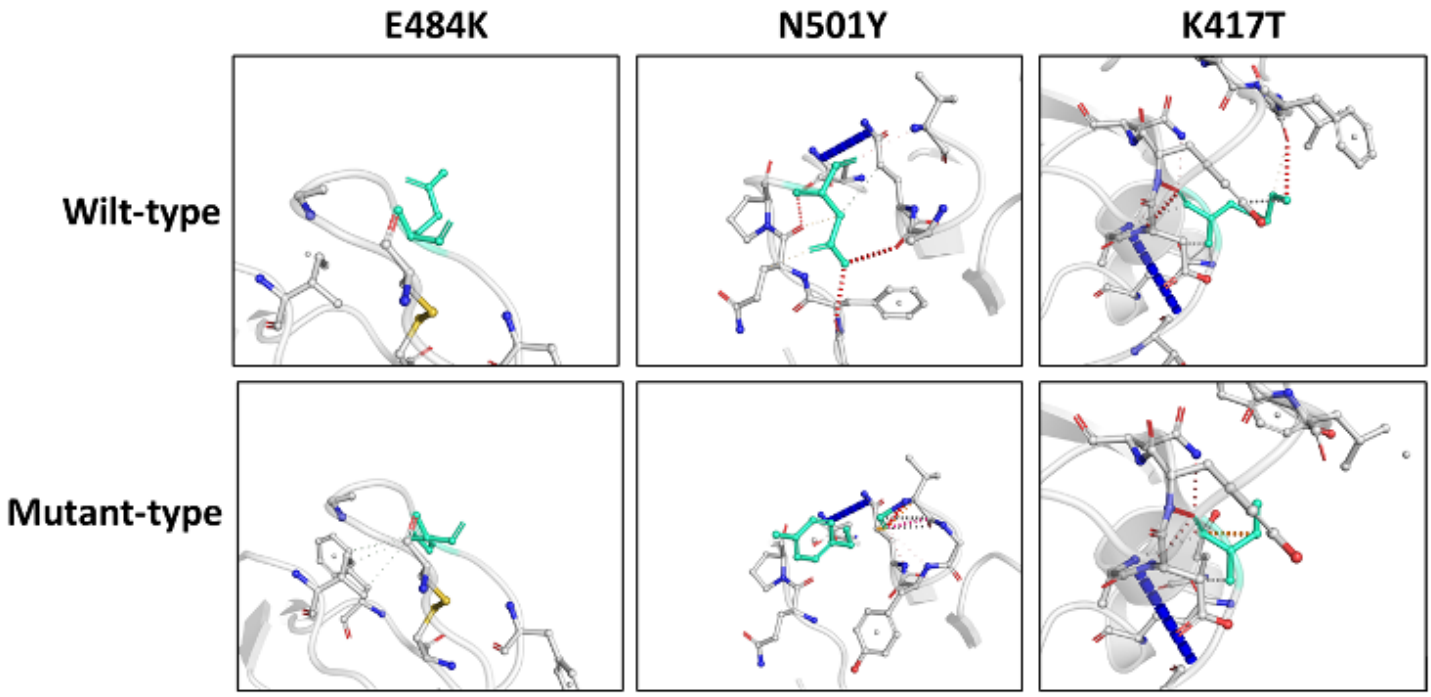

Figure 1

Prediction of intermolecular interactions in response to substitutions E484K, N501Y and K417T of Spike protein. Wild-type and mutant residues are colored in light green. Hydrogen-bonds and hydrophobic interactions are represented in red and gray dash lines, respectively. Figures were obtained by DynaMut web-sever and re-analyzed in PyMol 2.3 (The PyMOL Molecular Graphics System, Version 2.0 Schrödinger, LLC).