



# Effect of Genomic and Amino Acid Sequence Mutation on Virulence and Therapeutic Target of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS COV-2)

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**Abstract:** The COVID-19 pandemic is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). It is one of the RNA coronaviruses which share the highest mutation rates of RNA viruses when compared with that of their hosts. The collective mutation rate of RNA viruses is up to a million times higher than their hosts and is correlated with enhanced virulence of viruses. The RNA, genomic material of SARS-CoV-2, has the capacity of showing amplified fast changes as the infection spreads. These changes were frequently observed in genes for spike glycoprotein, nucleocapsid, ORF1ab, and ORF8, together with RNA dependent RNA polymerase. In contrast, genes for envelope, membrane, ORF6, ORF7a and ORF7b showed no observable changes in terms of amino acid substitutions. Mutated SARS COV-2 at these particular sites has been associated with viral infectivity, false laboratory results and viral genome mutation and interferes with therapeutic targets. Interferences with therapeutic targets is frequently observed in genes for RdRp. Additionally, mutated viral genes for RdRp render slow fidelity of RdRp protein, resulting in a high mutation rate. Such a high mutation rate might allow new virulent forms of the virus to emerge and influence the disease profile. This review aimed to elaborate on the effect of genomic and amino acid sequence mutations on the virulence and therapeutic targets of SARS COV-2. To achieve this objective, multiple literatures have been reviewed.

**Keywords:** genomic mutations, amino acid sequence mutations, virulence, therapeutic target, RdRp, SARS COV-2, spike proteins

## Introduction

### Background Information

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is an RNA coronavirus belonging to genus  $\beta$ -coronavirus and a member of the family of Coronaviridae.<sup>1</sup> Most Coronaviridae families, including those causing respiratory problems in human hosts, are belonging to two genera,  $\alpha$ -coronavirus and  $\beta$ -coronavirus. The extent of respiratory problems differs from person to person. For instances, it causes mild infection in healthy adults but has much more severe effects in the elderly and patients with co-morbidities. The later can experience severe damage to their respiratory systems, sometimes dying as a result.<sup>2</sup> Several literatures indicated that people older than 65 years and those with underlying co-morbidities experience higher mortality rates than former ones.<sup>2,5-7,9-11</sup>

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Fever, cough, shortness of breath and fatigue are common symptoms of the coronavirus disease (COVID-19), caused by SARS COV-2.<sup>3,4</sup> As indicated in early data, about 20% of patients developed severe symptoms of COVID-19 accompanied by shortness of breath and requiring hospitalization, including 5% who are admitted to intensive care units. Besides, the initial estimate of case fatality rates from COVID-19 was from 3.4% to 6.6%, which was much externally lower than the 9.6% for severe acute respiratory syndrome (SARS) or the 34.3% for Middle East respiratory syndrome (MERS).<sup>5–7</sup>

Regardless of the fact that the outbreak has dramatically expanded to create a global pandemic,<sup>8</sup> the COVID-19 related morbidity, numbers of active cases, and mortality rates differ from country to country. Many studies from different corners of the world speculating on possible reasons for these variations but have produced no credible results, yet. According to different studies from different corners of the globe, the 4715L variant of open reading frame 1ab (ORF1ab) protein, 614G variant of S protein and RNA dependent RNA polymerase (RdRp) were the commonest viral proteins affected by mutations among others.<sup>12,13</sup> One study hypothesized that there is a correlation between mutations at the 4715L variant of ORF1ab and 614G variant of S protein and fatality rates.<sup>12</sup> Moreover, mutated RdRp may allow the viruses to escape host immunity and to develop resistance to commonly used antiviral therapies.<sup>13</sup> Therefore, dealing with the effects of mutation on virulence and therapeutic targets of this virus should be needed to overcome such challenges, hence, the aim of this review was to shed light on the effects of genes and amino acid sequence mutation on virulence and therapeutic targets of SARS COV-2.

## SARS COV-2 Genome and Genomic Expression

SARS-CoV-2 has a single strand RNA genome, which is positive-sensed and about 29,903 kb nucleotides long, making it as one of the largest genomes among RNA viruses.<sup>14</sup> These nucleotides are organized into 10 ORF-genes encoding for 28 proteins. Four out of 28 proteins are structural proteins (spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins), 16 are nonstructural proteins (Nsps) and 8 are accessory proteins.<sup>14–16,24</sup>

The spike (S) glycoprotein is comprised 1273 amino acid residues and is critical for the viral infection. It has N-terminus signal peptide of 1–13 amino acid residues, S1

subunit peptide of 14–685 amino acid residues, and S2 subunit peptide of 686–1273 amino acid residues.<sup>18–20</sup>

The S1 subunit peptide has N-terminal domain (composed of 14–305 stretch of amino acid residues) and a receptor-binding domain (RBD) (composed of 319–541 stretch of amino acid residues). The S2 subunit peptide has a fusion peptide (FP) (composed of 788–806 stretch of amino acid residues), a heptapeptide repeat sequence 1 (HR1) (composed of 912–984 stretch of amino acid residues), an HR2 (composed of a 1163–1213 stretch of amino acid residues), a transmembrane domain (composed of 1213–1237 stretch of amino acid residues), and a cytoplasmic domain (composed of 1237–1273 stretch of amino acid residues).<sup>18</sup>

The virus to host interaction is initiated when S glycoprotein, through its RBD of S1 subunit peptide, interacts with angiotensin-converting enzyme-2 (ACE-2) receptor on the host cell surface. The RBD-ACE-2 interaction allows not only viral infection, but also enhances rapid human-to-human transmission.<sup>19,21</sup> Mutation of these sites do have effect on viral virulence.<sup>22</sup>

The other site on the viral genome prone to mutation is ORF1ab, encoding for two viral polypeptides (Pp1a and Pp1b), which generate 16Nsps after cleavage by chymotrypsin-like (3CL) protease (M<sup>pro</sup>) and papain-like proteases.<sup>19,23,24</sup>

## Gene and Amino Acid Mutations of SARS COV-2

### Gene Mutations

RNA viruses overwhelms their immediate hosts in mutation rates which was highly correlated with enhanced virulence of virus.<sup>25</sup> The SARS-CoV-2 genome showed increasing fast and frequent changes at the level of genes for S, N, ORF1ab ORF8 proteins as the spread of infection amplified.<sup>21,26</sup>

Study done on six geographic regions by taking SARS-CoV-2 as the reference identified a total of 1234 mutations.<sup>12</sup> Another study done in USA analyzed the rate of accumulated viral gene mutations and identified accumulated mutations on genes for helicase, NSP2, S, NSP3, RdRp, ORF3a, ORF8, and N proteins.<sup>17</sup>

### Amino Acid Mutations

#### Amino Acid Mutations for Structural Proteins

The S protein depicted substitutions of D614G, V483A, L5F, Q675H, H655Y, and S939F, with D614G mutation identified as the most common amino acid mutations

among others.<sup>21</sup> Similarly, R203K and G204R mutations are commonly identified at the level of N proteins.<sup>21,33</sup> There are no mutations identified yet in relation to M and E proteins. The possible reason might be housekeeping functions of these proteins allowing them to have a greater resistance to mutations.<sup>21</sup>

### Amino Acid Mutations for Non-Structural Proteins

ORF3a, N, ORF8, ORF1ab, and S proteins showed the largest number of non-synonymous mutations, with ORF3a taking the leading position.<sup>21,34</sup> The Q57H and G251V mutations account for the majority of non-synonymous mutations identified in ORF3a. Similarly, L84S is a major non-synonymous mutation in ORF8, accompanied by a change in V62L.<sup>21</sup>

Comparable levels of mutation frequencies have been observed at the level of NSP2, NSP3 and RdRp proteins with that of ORF3a, N, ORF8, ORF1ab and S proteins.<sup>21</sup> The nsp2 (Asp268del) deletion mutation is the most common and widely spread type of non-synonymous mutation across Europe.<sup>57</sup> Like E and M structural proteins, ORF6, 7a, 7b and 10, NSP7, NSP9, NSP10, and NSP11 proteins showed no significant changes in amino acid residues, yet.<sup>21,35</sup> The 27-amino-acid deletion in ORF7a SARS-CoV-2 reported in Arizona was exceptional.<sup>56</sup>

## Impact of ORF1ab Gene Mutation in Laboratory Results and Amino Acid Sequences of Encoded Proteins

ORF1ab occupies more than 75% of the SARS COV-2 genome and is identified as the highest mutation frequency region.<sup>17,27</sup> In Japan, three and twenty-four nucleotide deletion mutations were identified within this region, and in Australia, twenty-nine mis-sense mutations were identified in the ORF1ab polyprotein.<sup>23</sup>

False positive laboratory result, as it permit infected individuals to live with other people and, might have an unfavorable impacts on endeavors to control the spread of the virus.<sup>28</sup>

Currently accepted laboratory test for SARS-CoV-2, the real-time polymerase chain reaction (RT-PCR) test, risks producing inconsistent results. The possible reasons for this inconsistency might be mutations in viral RNA sequences affecting RT-PCR-utilizing primers in different genes; or mutations in the primer and probe target regions; or genetic diversity and rapid evolution of SARS-CoV-2 that have been observed in different studies.<sup>29</sup>

The 14,408C>T (P4715L) and 3037 C>T (F106F) variants have been recognized as the two most frequently occurring gene mutations at ORF1ab regions, possibly leading to inconsistent RT-PCR test results. The P4715L variant was causing mutations in the RdRp/NSP12 and responsible for lower replication fidelity of the enzyme. The F106F variant, on the other hand, was causing mutations in the Nsp3 gene.<sup>30,31</sup>

Furthermore, ORF1ab regions of the virus from different geographic regions showed mutation of amino acid sequences of encoded proteins. An isolate from China showed N2708S and F2908I, whereas from South Korea and Sweden showed G818S and F4321L. On the other hand, an isolate from Brazil showed L3606F and from Vietnam showed R3323C.<sup>32,58</sup>

## Effect of Mutant Spike Protein on Virulence of SARS COV-2

The affinity of RBD of the S sub-unit peptide of the S protein for ACE-2 and the overall infectivity of the virus has been potentially altered by gene mutations for spike.<sup>23,36</sup> The overall impact is either reduced<sup>20,37,38</sup> or enhanced virulence of the virus depending on the site of mutation.<sup>38-42</sup>

Aspartate to glycine mutation (D614G) of the S protein was thought to be 10-times more virulent than the original strain from China (Wuhan-1).<sup>38,39</sup> Patients infected by the D614G mutant variant had advanced viral loads,<sup>43</sup> and the overall disease progress was severe when compared with original China (Wuhan-1) strain-infected patients.<sup>22</sup> The possible explanation might be related to the higher affinity D614G mutant strain for ACE2 than the original China (Wuhan-1) strain.<sup>44</sup>

Furthermore, the potential electro-static change from polar-aspartate to non-polar-glycine on the surface of D614G mutant S protein creates a favorable environment for mutant variants in a hydrophobic pocket of the S protein. Moreover, the change from large-aspartate residue to small glycine residue on the D614G mutant variant might increase the flexibility of a smooth switchover from the inactive DOWN state to the active UP state.<sup>21,39,41</sup> Additionally, D614G facilitates cleavage of the spike protein by host proteases and thereby enhances membrane fusion, which is critical for viral entry into host cells.<sup>39,42</sup>

Similar to D614G, V367F, W436R, and D364Y are three other mutant variants of S protein emerging in Wuhan, Shenzhen, Hong Kong, and France. These variants have

enhanced structural stabilization of the RBD beta-sheet scaffold and also displayed a higher affinity for human ACE2 just like to D614G variant of the S protein.<sup>40</sup>

In contrast to D614G and other mutations which enhance infectivity of the virus, there are also mutations which reduce it, such as glycosylation mutants (N331 and N343) mediating protein folding and stability, and amino acid mutation in RBD (R408I). Glycosylation and RBD mutants together lead to drastically reduced viral infectivity.<sup>20,45,46</sup>

R408I mutation seems to disrupt the 408R-glycan hydrogen bond by changing hydrophilic arginine residue with hydrophobic isoleucine residue with no hydrogen-bond potential. As evidence for reduced viral infectivity, potentially reduced ACE2 binding affinity which led to reduced virulence of the virus was observed with the R408I mutant strain identified in India.<sup>20</sup>

## Effect of Mutant RdRp on Gene Mutation and Therapeutic Target

ViralRdRp, also known as NSP12, is the complex protein with multiple domains that performs viral RNA synthesis and genome duplication.<sup>47</sup> An RdRp mutation, particularly in position 14408, makes a great contribution to overall increased viral genome mutation rates. There are also reports on the mutation of P323L in RdRp,<sup>13,30</sup> which could result in structural rigidity of the protein and consequently lower replication fidelity of RdRp.<sup>31</sup>

Lower fidelity of RdRp also leads to higher mutation rates of the virus within host cells, which in turn allows new virulent forms to emerge and influence disease profile.<sup>31,48</sup> Moreover, mutant SARS COV-2 at P323L in RdRp has made infected COVID-19 patients to develop much more severe symptoms.<sup>22</sup>

In addition to its contribution to increased viral genomic mutation rates, mutant RdRp might affect the efficacy of antiviral drugs and thereby disturb therapeutic targets. Antiviral drugs such as remdesivir via their active component (adenosine nucleotide analog) binding to the active sites of RdRp and are being considered potential therapeutic options through viral replication inhibition.<sup>27,47,49</sup> The active component of remdesivir binds to the RdRp catalytic site and halts nucleic acid elongation. Binding affinity with remdesivir profoundly decreased in several mutants, particularly F480L and V557L variants, strongly suggesting drug resistance.<sup>53–55</sup>

Mutation of RdRp at A97V, A185V and P323 causes alteration of the secondary structure of RdRp. In mutation of RdRp at A97V and A185V, valine (with a relatively larger side chain than alanine) substitutes the alanine (with a relatively smaller side chain than valine) amino acid. In mutation of RdRp at P323L, the proline (with a bulky pyrrolidine ring side chain) substitutes by leucine that might result in loss of the structural integrity of the protein.<sup>47,48</sup>

Recent studies on virtual molecular docking identified many drugs as SARS-CoV-2 RdRp inhibitors, including Simeprevir, Filibuvir, and Tegobuvir.<sup>49,50</sup> The P323L and L329I mutations of RdRp were identified very close to the docking site, probably interfering with the interaction of these drugs with RdRp.<sup>47,49–53</sup>

## Conclusion

The causative agent of the COVID-19 pandemic is prone to a high mutation rate, which leads to changes in the properties of the virus, including its virulence or infectivity, and resistance to antiviral drugs. For instance, mutated SARS COV-2 in S protein at D614G infects ACE2 expressing cells more efficiently, and these boost its virulence. Thus, a patient infected by a mutant variant has higher viral loads and develops more severe symptoms of COVID-19.

Mutated SARS COV-2 at RdRp regions causes low fidelity of RdRp, resulting in higher mutation rates, which in turn lead to the emergence of new virulent strains, influence overall disease profile and interfere with RdRp-targeting pharmacological agents.

Even though a number of genome sequences of this virus have been identified and published, by no means all countries have sequenced the viral genome as yet, information which is important for recognizing mutated genes and newly emerging virus properties.

## Copyright/Ethical Concerns

Since this is a review article, there are no ethical concerns related to it.

## Disclosure

The authors report no conflicts of interest in this work.

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