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SARS-CoV AND SARS-CoV-2: A Genomic and Phylogenetic Comparison

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Abstract: *COVID-19 pandemic caused by the SARS-CoV-2 coronavirus shifted attention towards all the types of coronaviruses that have emerged in the last few years and have shown their presence among humans. These include SARS-CoV, MERS and SARS-CoV-2 causing severe symptoms in humans and some other coronaviruses that cause fevers and common respiratory symptoms. Two of the most important viruses that have caused severe symptoms in humans are the 2003 coronavirus SARS-CoV and the 2019 coronavirus SARS-CoV-2. Here, we have gone through the various similarities and dissimilarities of the two viruses in terms of their origin, phylogenetic background, structure, genomic composition as well as the immune response the body shows against infection due to these coronaviruses. This gives a detailed description of the difference based on the presence of the two viruses in different clades in the evolutionary study. It also shows that the two viruses are distinct in terms of the genomic composition and the response provided by the immune system when these viruses infect a human body. This difference is a major reason behind the high transmissibility and severity of SARS-CoV-2 compared to SARS-CoV.*

Keywords: *SARS-CoV, SARS-CoV-2, Open reading frames (ORF), Angiotensin converting enzyme-2 (ACE-2), Spike protein*

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I. Introduction

Coronaviruses are a diverse group of viruses that infect a wide range of species, as well as humans, and can cause mild to serious respiratory infections. Extreme acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome (MERS), both extremely virulent zoonotic coronaviruses, were first discovered in humans in 2002 and 2012, respectively, and caused deadly respiratory illnesses **[1]**.

SARS-CoV-2, a new coronavirus, was discovered in the city of Wuhan in China towards the end of 2019 and caused an outbreak of atypical viral pneumonia. Due to its great transmissibility, this unique coronavirus illness, also known as coronavirus disease 2019 (COVID-19), has spread swiftly over the world **[2,3]**. It has surpassed SARS-CoV and MERS in terms of both the number of infected persons and the number of deaths.

SARS (Severe Acute Respiratory Syndrome) was caused by the SARS-associated coronavirus (SARS-CoV) **[4]**. SARS-CoV 2, the virus that causes COVID-19 infection, is identical to SARS-CoV **[5]**.

There are seven different types of coronaviruses that affect the humans **[6]**. The three most important coronaviruses causing severe symptoms in humans are:

1)SARS-CoV
2)Middle East Respiratory Syndrome (MERS)
3)SARS-CoV-2

Coronaviruses are originated in animals but were transmitted to humans, therefore they are called as zoonotic organisms.

Since their bodies are adapted to the infection, certain animals can bear the virus without being ill and are hence most likely to be immune. Hence, animals are a trusted source of emerging infectious diseases, according to the Centers for Disease Control and Prevention (CDC) **[7]**.

Viruses, on the other hand, are vulnerable to mutation. When a virus mutates as a result of cross-species contact, it becomes unstable and potentially hazardous.

This review summarizes the various similarities and dissimilarities between the SARS-CoV and SARS-CoV-2 viruses by analyzing their various characteristics.

II. Coronavirus and its types

Coronaviruses are positively stranded RNA viruses with an envelope and with spike proteins present on their surface, just like a crown (hence the name Coronavirus where Corona in Latin means Crown) **[8]**.This spike protein on its surface has the ability to bind Angiotensin converting enzyme-2 (ACE-2) **[9]**. Though Coronavirus originated in bats, it has an ability to affect a variety of organisms including humans, like SARS-CoV which causes respiratory distress in humans **[8]**. Coronavirus belongs to the family of Coronaviridae with the subfamily being Orthocoronavirinae and the subgenus sarbecovirus. Coronavirus can be categorized to be a part of the kingdom of Orthornavirae, phylum of Pisuviricota, Class of Pisoniviricetes, and order of Nidovirales **[10-12]**.

There are 4 main types of coronaviruses including Alpha-coronavirus, Beta-coronavirus, Gamma-coronavirus and Delta-coronavirus **[8]**. The Alpha and the Beta genera of the Coronavirus have the ability to infect mammals while the Gamma and the Delta genera are avian coronaviruses affecting the birds **[12]**. Among the mammalian coronaviruses, there are seven coronaviruses that can affect humans, with four of them showing low susceptibility **[8,12]**. These four include HCoV-229E and HCoV-NL63 of the Alpha-coronavirus genera, and HCoV-HKU1 and HCoV-OC43 of the Beta-coronavirus genera **[8,12]**. The other three coronaviruses MERS, SARS-CoV, and SARS-CoV-2 have proved to be severe and often fatal to the human population, all of them belonging to the Beta-coronaviruses genera **[8]**.

The coronavirus present in bat, CoV-RaTG13, has a genome sequence 96.2% identical to the SARS-CoV-2 and 79.5% similar to the SARS-CoV **[12,13]**. Both SARS-CoV and SARS-CoV-2 utilize their spike proteins to bind to the Angiotensin converting enzyme-2 (ACE-2) receptor present on the cells in order to infect the host and multiply inside the host genome **[9,11,13]**.

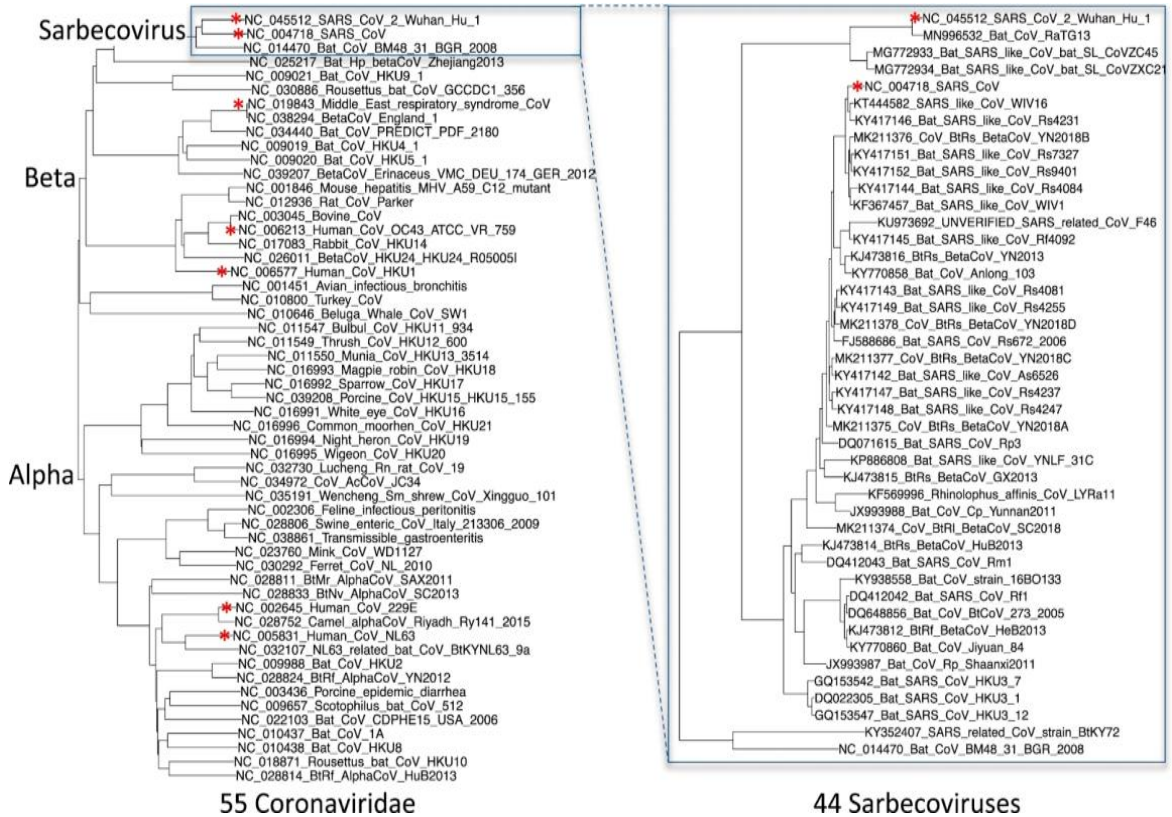

Figure 1 Left- Phylogenetic representation of Orthocoronavirinae, red asterisk represents coronaviruses that infected humans. **Right-** Phylogenetic representation of the genome of Sarbecoviruses **[11]**

III. Phylogenetic Tree

Phylogenetic Tree uses morphological, anatomical and genetic differences to represent the evolution of a species from a common ancestor in the form of a tree **[14]**. In the case of a phylogenetic tree of a virus, it represents the novel viral lineages that have developed due to evolutionary changes in the viral genome **[14]**. The phylogenetic tree was initially represented using the Supertree method which did not provide fruitful results in case of viruses and hence was later replaced with the matrix representation with parsimony (MRP) pseudo-sequence supertree analysis to carry out phylogenetic analysis **[15]**.

SARS-CoV and SARS-Cov-2 are both beta viruses that have proven to be harmful for humans, but based on the Supertree analysis, they occupy different positions in the phylogenetic tree and hence are a part of different lineages based on genome sequence analysis of both the coronaviruses **[11,14,15]**. A major reason behind this is the absence of any orthologous genes in the ORF8 of SARS-CoV and SARS-CoV-2 which leads to divergence in the phylogenetic tree **[15]**.

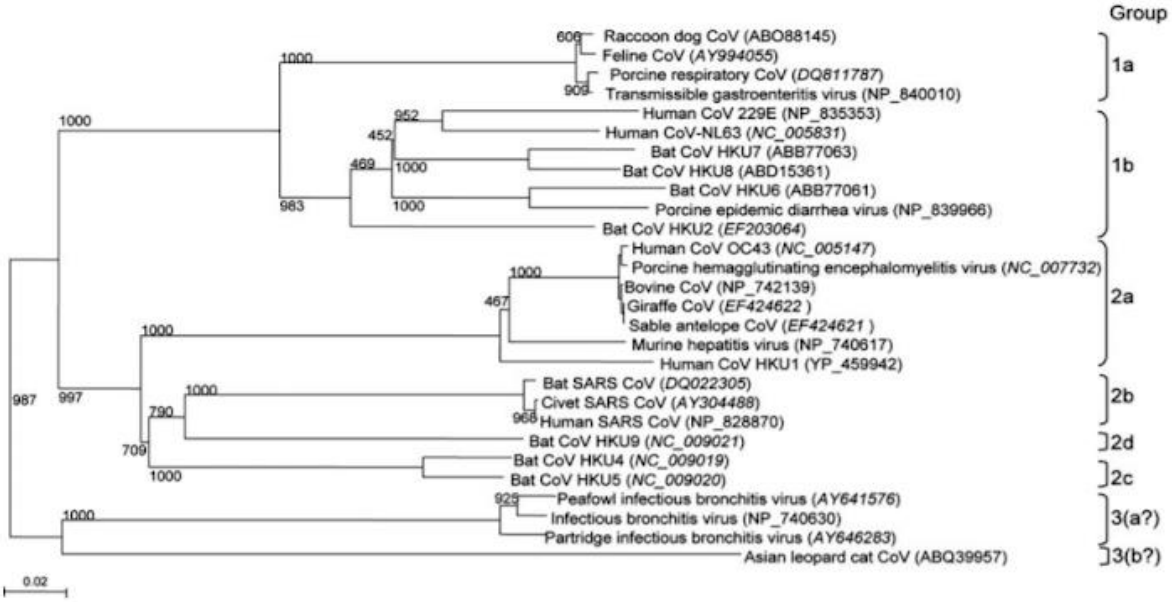

Figure 2 Phylogenetic tree of the different Coronaviruses affecting different species **[10]**

The Figure 3 represents the methodology utilised in order to implement the MRP pseudo sequence supertree to phylogenetically differentiate between SARS-CoV and SARS-CoV-2 **[15]**. This method is successful in establishing the fact that SARS-CoV and SARS-CoV-2 belonged to two different branches of the phylogenetic tree representing two different clades in evolutionary analysis **[15]**. In this procedure, there are 4 major steps:

The OrthoMCL program was used to organize some selected coronaviruses in ten groups of CDS for orthologous proteins. This was followed by aligning by Multiple Alignment using Fast Fourier Transform (MAFFT) using the L-INS-i method, and ultimately forming the Phylip file with the help of Clustal W.

Phylogenetic trees were built based on these CDSs and bootstrap replications using the ML phylogenies of PhyML.

Custom made scripts were applied after assigning A or T to the members of each clade to retrieve the Baum-Ragan matrix pseudo-sequences **[15]**.

These sequences were then used to create a Phylogenetic supertree using PhyML by assuming the A or T substitutions to be equal **[15]**.

This established the fact that even the closest ancestors of the SARS-CoV and SARS-CoV-2 are different, separating them completely from each other **[15]**. While the SARS-CoV has the civet coronavirus AY572035 as its closest relative, SARS-CoV-2 has RaTG13 isolated from bat Rhinolophus affinis (Yunnan, China) as its closest relative based on the five CDSs of ORF1ab, spike protein, N protein, ORF6 and ORF7a and bat coronavirus MG772933 and MG772934 isolated from bat Rhinolophus sinicus as its closest relatives based on M protein, ORF3a, and ORF8 **[11,15]**.

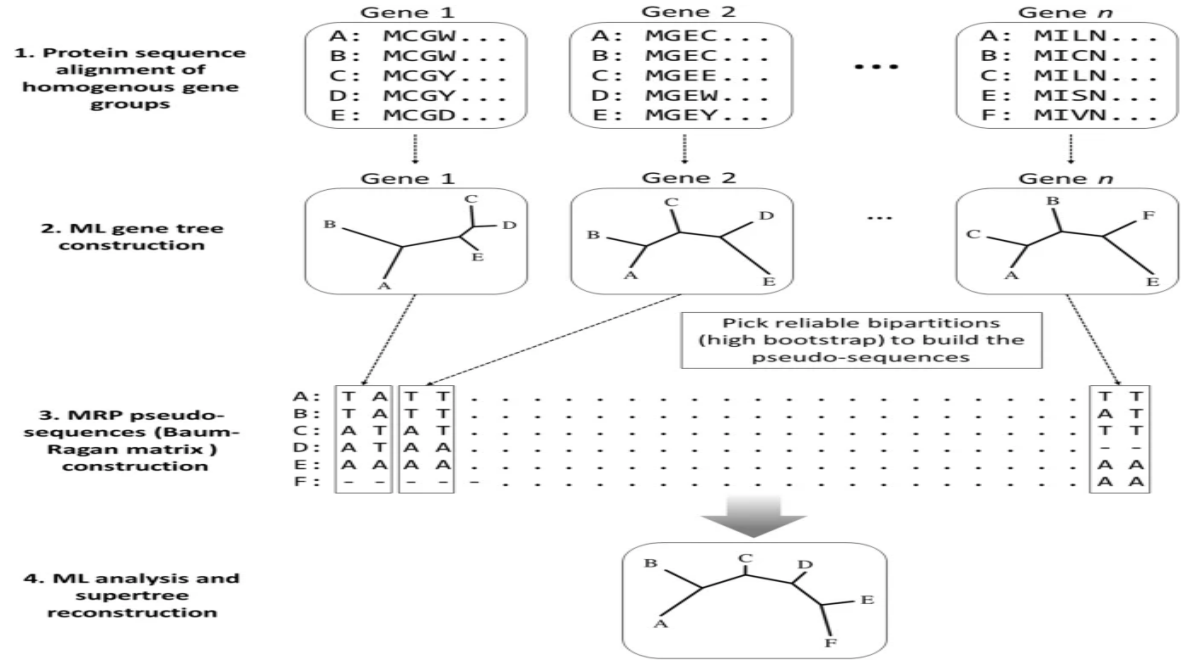

Figure 3 Representation of the methodology utilized in order to implement the MRP pseudo sequence supertree to phylogenetically differentiate between SARS-CoV and SARS-CoV-2 **[15]**

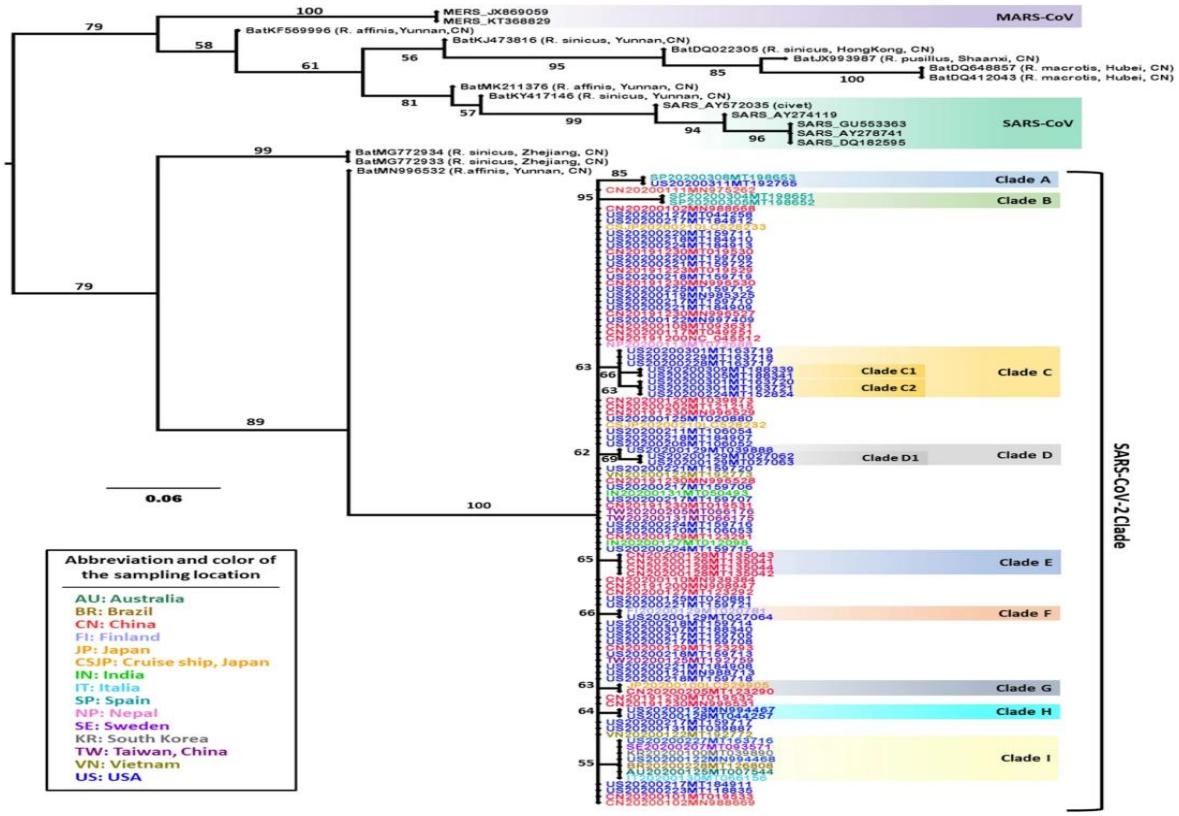

Figure 4 MRP pseudo-sequence supertree for SARS-CoV-2, highlighting the clades for different coronaviruses like SARS-CoV, SARS-CoV-2, MERS, etc. **[15]**

IV. Genomic Composition & Virion Structure

The various types of coronavirus (CoV) have similar virion structures. They are composed of four major structural proteins namely, nucleocapsid, membrane, envelope, and spikes **(Figure 5)**. The different CoV strains have a common genetic organization for the coding region encoding for a canonical set of genes in the order 5′ end- Open reading frames (ORF) 1a/b replicase, spike, envelope, membrane, nucleocapsid-3′ end

(Figure 6), although the number and location of accessory ORFs present in different CoV species vary (6–11 ORFs) **[16]**. Subgenomic (sg) mRNAs, which are responsible for gene translation, form a nested set with the viral genome at the 5′ and 3′ ends. Along with subgenomic mRNAs, a common 5′ leader sequence and a 3′ terminal sequence are present **[17]**. The genome has small untranslated regions (UTRs) at both 5'and 3'ends. The viral genome also encodes several nonstructural proteins (nsps) including RNA-dependent RNA polymerase (RdRp), coronavirus main protease (3CLpro), and papain-like protease (PLpro) **[18]**.

At least six ORFs make up a typical CoV genomic and subgenomic sequence. Except for gamma-CoVs, which lack nsp1, the first ORF (ORFa/b) encodes 16 non-structural proteins (1–16 nsp) that account for over 67 percent of the viral genome **[17].** The two protease domains conserved in all types of CoVs encoded by the ORF1a sequence in the genome are a papain-like protease (PL2pro) in nsp3 and a 3C-like protease (3CLpro), also known as the "main protease" in nsp5 **[19]**.

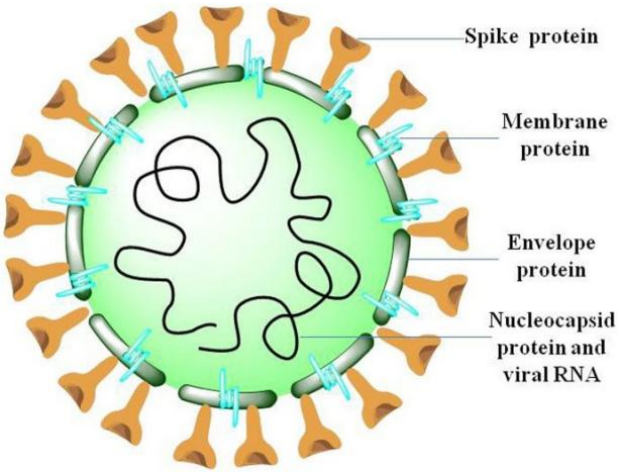

Figure 5 The CoV Structure: Composed of S (spike), M (membrane), E(envelope) and N(Nucleocapsid) **[17]**

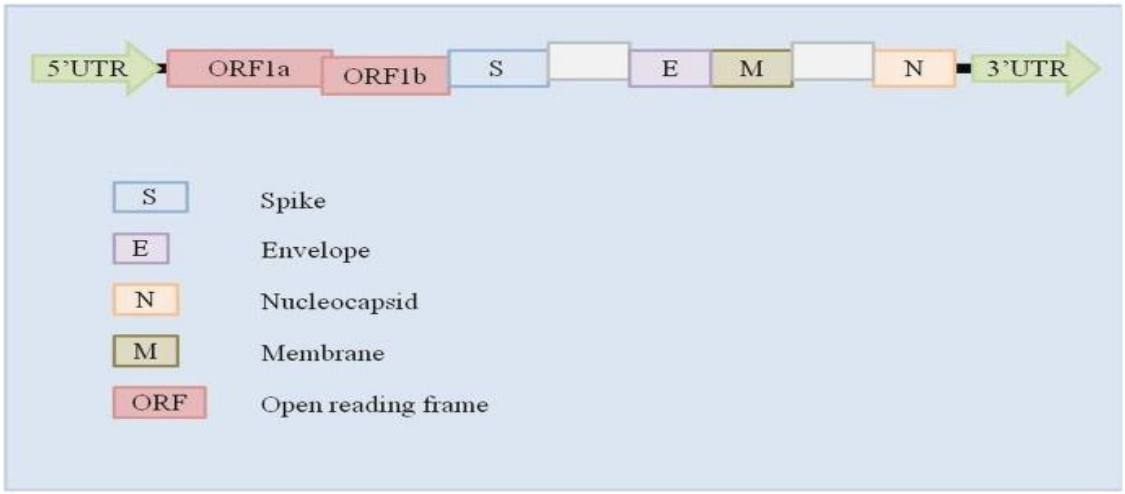

Figure 6 Genomic organization of CoVs **[17]**

V. Distinct Features Of SARS-CoV And Novel Coronavirus SARS-CoV-2

Structural Comparison: Amino acid substitutions in SARS-CoV-2

The analysis of the structural and functional differences in SARS-CoV and SARS-CoV-2 depends on the amino acid alternatives in different proteins.

Between the amino acid sequences and the matching consensus sequences of SARS-CoV and SARS-CoV-2, 380 amino acid substitutions occurred **[17]**. The amino acid sequences in the envelope, matrix, or accessory proteins p6 and 8b, nsp7, and nsp13 showed no change **[17]**. nsp2 and nsp3 are non-structural proteins with single amino-acid substitution at positions 61 and 102, respectively **[20]**. Additionally, 7 substitutions were seen in structural proteins (ORF2-S, ORF3a, ORF5-M, ORF8, and ORF9-N) and one in the ORF1ab, specifically in nsp6 **[21]**. Spike protein was shown to have 27 amino acid substitutions totaling 1273 amino acids, including six alterations in the receptor-binding domain (RBD) and another six in the underlying subdomain's (SD) amino acid region 569–655 **[17]**. Interestingly, Asp614Gly in the spike protein (ORF2-S) was the only substitution that

became fully predominant **[21]**. Also, the receptor-binding subunit S1 domain has four substitutions (Q560L, S570A, F572T, and S575A) **[22]**.
With no amino acid substitutions, the receptor-binding motifs that interact with the human ACE-2 receptor were discovered to be identical to those reported in the SARS-CoV strain **[22]**.
On examination of the location of these substitutions, it was found that most of them correspond to residues that were conserved in SARS and related beta coronaviruses **[21]**.
These amino acid substitutions makes the SARS-CoV-2 different from SARS-CoV strain. Further study on these substitutions might help us in understanding the features of SARS-CoV-2 further.

Genomic Comparison

The SARS-CoV and SARS-CoV-2 strains show extremely high homology at the nucleotide level. However, there are six locations in which the genomes of these two strains vary from one another. The first three variations are seen in the partial coding of ORF1a/b (448 nt, 55 nt, and 27 8nt, respectively). The partial coding sequences of the S gene (315 nt and 80 nt, respectively) are the next two areas of variation, while the ORF7b and ORF8 genes' (214 nt) part of coding sequences is the last **[23]**.

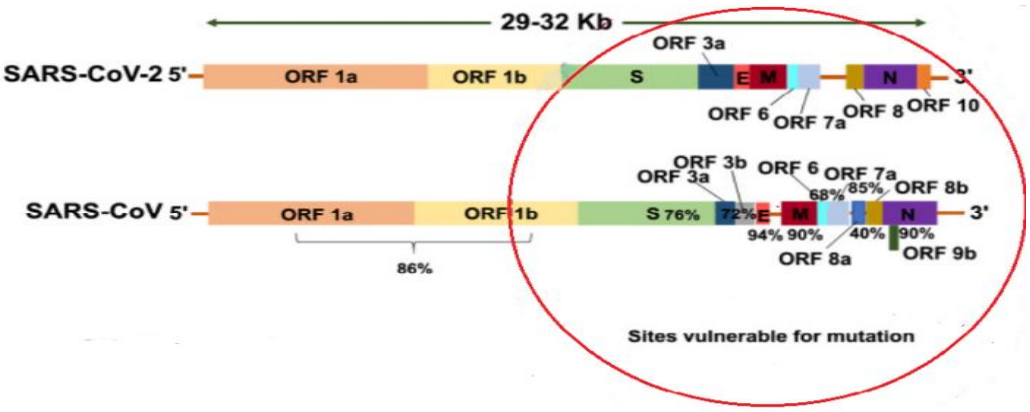

Figure 7 Comparison of SARS-CoV and SARS-CoV 2 viral genome **[25]**

Proteomic similarity analyses of SARS-CoV and SARS-CoV-2 show that most of the proteins are highly homologous (95%-100%) **[17]**. Even though the genomes of RdRp and 3CLpro protease are only 82% identical, the two strains have approximately 95% sequence similarity **[24]**. Furthermore, S proteins, a highly conserved receptor-binding domain (RBD), and a domain of S protein of both these strains have 76% of sequence similarity **[24]**.
SARS-CoV 2 does, however, have two proteins (ORF8 and ORF10) that are unrelated to the SARS-CoV strain **[17]**. The amino acid sequence of ORF8 obtained from SARS-CoV-2 differs from the SARS-CoV conserved sequences.
Therefore, further study of the functions of the proteins ORF8 and ORF10 can be beneficial in understanding more about the SARS-CoV strain.

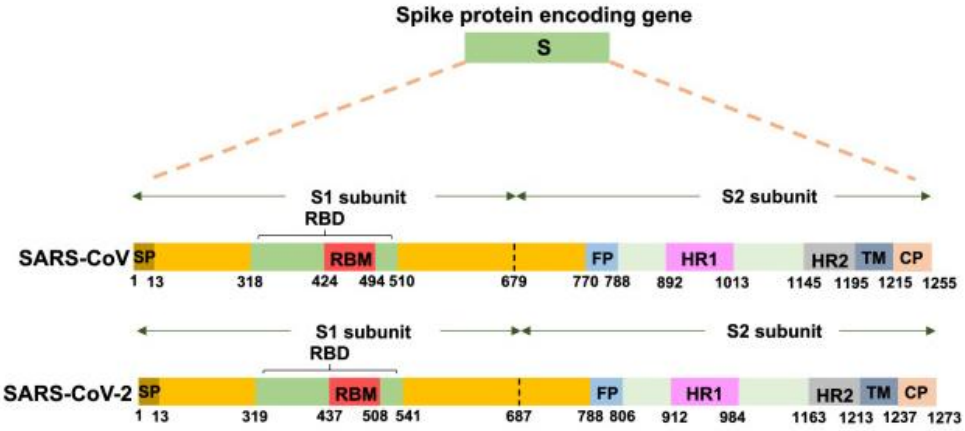

Figure 8 Comparison of the spike protein (S) of SARS-CoV and SARS-CoV-2 **[25]**

VI. Viral Comparison: Transmissibility And Incubation Period

Factors	SARS-CoV-2	SARS-Cov
Transmissibility, R_0	2.5	2.4
Incubation period, days	4-12	2-7
Interval between onset of symptom and infection, days	0	5-7
Transmissibility with mild illness or no symptom	High	Low
% of patients requiring hospitalization	Few (20%)	Most(>70%)
% of patients requiring intensive care	1 out of every 16000	Most (>40%)

Table 1 Comparison between SARS-CoV-2 and SARS-CoV based on their infectivity, incubation period and their transmissibility **[26-28]**.

Interpretation of Table 1:

The analysis of the ability of a new pathogen to spread and infect determines the severeness of the disease outbreak.

R0 is defined as the average number of transmission from one infected person **[29]**. R0 > 1 depicts that the epidemic is spreading. The R0 for SARS-CoV-2 was estimated as 2.5 whereas R0 for SARS-CoV was 2.4. This interprets that SARS-CoV-2 has more transmissibility than SARS-CoV, making it more widespread.

SARS-CoV-2 has a longer incubation period, therefore, SARS-CoV epidemics form slower.

Another important difference between SARS-CoV and SaRS-CoV-2 is their virus shedding. SARS-Cov has more affinity towards the lower airways than the upper respiratory tract. For SARS-CoV-2, the average viral load for the upper respiratory tract was more (6.8x105 copies per swab) **[30]**.

SARS-CoV-2 is harder to contain than SARS-CoV since it transmits the virus even before the onset of symptoms. Also, many SARS-CoV-2 infected patients do not show any symptoms but have a high transmission rate.

SARS-CoV is more severe since most of the patients required mechanical ventilation and intensive care compared to SARS-CoV-2 infected patients.

VII. Immune Response

SARS shows the extreme innate immune responses in humans. It is associated with short-lived B cell response and reduction in T cells within the human body **[31]**. There are some differences between SARS-CoV and SARS-CoV-2 based on the immune response they generate on infection.

Immune response to SARS-CoV

SARS-CoV upon initial infection are received by respiratory Dendritic cells (rDCs) that process the antigen and present it to the T cells via MHC Class 2 molecules **[31]**. T cells get activated and proliferate on receiving its attachment to the peptide-MHC complex via the T cell receptor and produce antiviral cytokines (IFN-γ, TNF-α, IL-2), chemokines (CXCL-9, 10 and 11) and cytotoxic molecules (perforin and granzyme B) **[31]**. Cytokines inhibit viral replication and enhance antigen presentation, while chemokines activate the innate and adaptive immune response and cytotoxins have a role to play in elimination of the infected cells and the antigen **[37]**. These are released as a result of a primary immune response to the pathogen **[31]**. Memory T cells are also activated, which release cytokines and chemokines to activate innate cells and more memory T cells, that reside in the tissue for protection against future infections by the pathogen. These memory T cells have an important role to play because the memory B cells and the antibodies have lower life span than memory T cells **[31]**.

The severe cases in SARS-CoV include leukopenia and lymphopenia and the loss of CD8 and CD4 T cells that inhibits efficient functioning of the T cells and hence affects the human immune system from working against the pathogen **[31]**. Severe cases also include effect on the antigen presenting cells like the dendritic cells **[38]**.

Neutralizing antibodies are induced by the Spike protein present on the surface of the SARS-CoV **[31]**. The T cell responses are induced by the N protein and the CD8 and CD4 T cells.

Immune responses have been observed to have persisted against SARS-CoV for upto 11 years after the first infection **[36]**.

Immune response to SARS-CoV-2

The SARS-CoV-2 virus infects cells in the lungs that express the ACE2 receptor, such as type 2 alveolar cells, via the naso-oral pathway **[32]**. As a result of unrestricted virus multiplication, these viruses decrease antiviral interferon (IFN) responses by avoiding innate immune cells.

Increased pro-inflammatory cytokines are produced as a result of the invasion of monocytes/macrophages, neutrophils, and other adaptive immune cells **[32]**. Th1/Th17 cell activation with viral epitopes may worsen inflammatory responses in the helper T cell subgroup **[33]**. This inflammatory reaction causes "cytokine storms," which cause immune-pathologies such as pulmonary edema and pneumonia **[33]**.

Neutralizing antibodies appear to be higher in patients who have had more severe illness. Patients with mild or asymptomatic COVID-19, on the other hand, had lower levels of neutralizing antibodies **[34]**. A study of more than 30,000 people with mild to moderate COVID-19 indicated that neutralizing antibody titres maintained for at least 5 months following SARS-CoV-2 infection **[35]**. It's probable that in people with low levels of neutralizing antibodies, the virus is cleared by the innate immune system and T cells(CD4+ and CD8+).Some research suggests that people who have been exposed to SARS-CoV-2 can establish virus-specific T cell responses without circulating antibodies.This could suggest that even in the lack of antibodies, those who have had moderate COVID-19 or were asymptomatic can generate memory T-cell responses to avoid repeated infection.

SARS-CoV-2 has been observed to have shown immune response against the infection to have persisted for beyond 4 weeks **[36]**.

VIII. Discussion

SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) and SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) have respectively affected the human population in 2003 and 2019 causing severe symptoms. Although these viruses belong to the same family and have a similar structure and virion structure, they are different in terms of their phylogenetic background, the immune response shown on infection, and their genomic composition. Both SARS-CoV and SARS-CoV-2 are Beta coronaviruses and use their spike proteins to bind Angiotensin-Converting Enzyme-2 receptor (ACE) in order to infect a host and multiply within the host. They both belong to different clades in the phylogenetic tree and have different closest ancestors separating them from each other in terms of their evolutionary relationship. SARS-CoV has its closest relative as a civet coronavirus while it is a bat coronavirus in the case of SARS-CoV-2. On the study of the genomic structure of the virus, we came to know that in SARS-CoV-2, most of the mutations took place in the structural proteins. Whereas, in SARS-CoV, mutations occurred in the non-structural proteins. With each evolution, we found that their complexity increased, thus resulting in high morbidity and mortality rates. It is also observed that the spike proteins (S) and their subunits S1 and S2 play a vital role in binding to the host cell receptors and promoting viral infection. These subunits also undergo mutations with each evolution.

So, we would like to conclude by stating that although SARS-CoV and SARS-CoV-2 are similar to each other when compared to other coronaviruses, yet they have unique features distinguishing them from each other.

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