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Insights into the Genomic Structure, Genetic Variants and Pathogenicity of Sars-Cov-2.

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ABSTRACT:

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has become a global health crisis, affecting economies and societies worldwide. Understanding the genomic structure and genetic variants of the virus is crucial for monitoring its evolution, guiding public health responses, and devising effective strategies to combat the pandemic. This review article aims to provide an in-depth overview of the current evidence on the genomic characteristics, genetic variants, and pathogenicity of SARS-CoV-2. We explore the viral genomic structure, key regions, and encoded proteins. Additionally, we discuss the diversity of genetic variants that have emerged during the pandemic.

Key words: Variants, Pathogenicity, SARS-CoV-2, genome

Introduction

Coronaviruses are a family of enveloped, positive-sense, single-stranded RNA viruses. The single-stranded RNA carries the genetic information necessary for viral replication and protein synthesis [1, 2]. The characteristic spike proteins on their surface give them a crown-like appearance, which is how they acquired the name "coronavirus" [3]. Bats are considered the natural reservoir hosts for many coronaviruses [4, 5]. They can harbor various coronaviruses without showing significant symptoms of the diseases caused by these viruses [6]. The close interaction between bats and other animals, as well as humans, can facilitate the spillover of coronaviruses into intermediate or secondary hosts [7, 8]. SARS-CoV, MERS-CoV, and SARS-CoV-2 (2019-nCoV) are among the most notable examples of coronaviruses that have evolved to infect the human respiratory tract and cause severe diseases [9, 10, 11]. COVID-19 disease is caused by SARS-CoV-2 infection. They are mainly divided into four sub-groups namely alpha, beta, gamma, and delta viruses of which Betacoronavirus genus are pathogenic to human [12, 13]. According to the International Committee on Taxonomy of Viruses and the World Health Organization on February 12, 2020, the virus first originated in China and quickly spread over the world, triggering a pandemic that infected 591 million individuals, causing about 6.4 million deaths worldwide [14]. The clinical presentation is typical of a flu-like condition of cough, fever, headache, sore throat, which in more critical cases can advance to a stage of dyspnea and pneumonia [15, 16, 17].

Understanding the genomic characteristics and genetic variants of the virus is essential for monitoring its evolution and devising effective control measures. In this review, we focus on the current evidence of SARS-CoV-2 genomic structure, genetic variants, and pathogenicity. This review article aims to provide an in-depth overview of the current evidence on the genomic characteristics, genetic variants, and pathogenicity of SARS-CoV-2.

Genomic Organization of SARS-CoV-2

SARS-CoV-2 is an RNA virus, which belongs to the Category Coronaviruses, Realm Riboviria, Order Nidovirales, Suborder Cornidovirineae, Family Coronaviridae, Subfamily Orthocoronavirinae, Genus Betacoronavirus and Subgenus Sarbecovirus [18, 19, 20]. SARS-CoV-2 shares some level of genome sequence identity with some members of betacoronavirures. It shares about 80% identity with SARS-CoV and about 50% with MERS-CoV [21]. Structurally the genome of the virus has a size of about 30kbp, which is responsible for encoding for the structural and nonstructural proteins of the virus [22, 23]. Eleven protein-coding genes and 12 expressed proteins make up the genetic composition of SARS-CoV-2, which has a guanine-cytosine composition of 38% [24, 25]. The SARS-CoV-2 viral genome has fourteen (14) open reading frames (ORFs). Out of these 14 ORFs, two-third of it encodes for the sixteen nonstructural proteins of the virus [26]. The other one-third of the ORFs codes for the four structural proteins (Spike (S) protein, envelope (E) protein, matrix protein (M) and nucleocapsid (N) protein) and the nine accessory proteins [27].

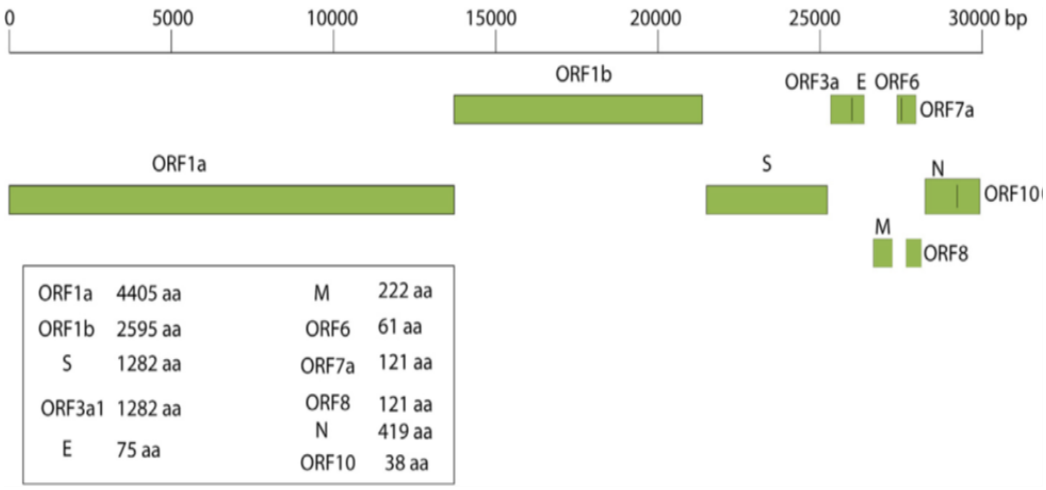

Figure 1: Genomic Structure of SARS-CoV-2 [28].

Structural Proteins of SARS-CoV-2 genome

SARS-CoV-2 has four significant structural proteins. These proteins are encoded by structural genes found in the region before the 3' end of the genome [29]. These structural proteins are essential for the assembly of the virion and the viral life cycle [27, 28, 30]. They facilitate viral entry, replication, assembly, and release, making them critical targets for antiviral therapeutics and vaccine development [31,]. Understanding the functions of these structural proteins is crucial for devising strategies to interfere with viral replication and spread, ultimately aiding in the control of COVID-19. The structure and the functions of the four structural proteins are summarized below:

Spike Glycoprotein (S)

The S protein of SARS-CoV-2 plays an important role in pathogenesis by using its receptor-binding domain (RBD) to bind to the host cell [28, 32,33]. The S protein is made up of 1273 amino acids, which upon synthesis forms three subunits videlicet S1, S2 and S2' which plays different roles during the attachment process to the host cell [33,34]. The S1 subunit is made up of RBD and N-terminal Domain (NTD), and its role is binding to ACE-2 of the human cell [33, 35, 36]. The S2 subunit acts as the fusion protein that aids in the fusion of the virus and the host cells membranes [37]. The S2' subunit of the S protein is where the host proteases cleave the S protein which aids in the activation of proteins which is crucial in fusion of the virus and host cell [38].

Envelope Protein (E)

The envelope protein is a small integral membrane protein with short N-terminal and C-terminal regions inside the virus. The envelope protein plays a role in viral assembly and release of the virus [38, 39, 40, 41]. It interacts with other viral structural proteins during the formation of the viral particle. Additionally, it is involved in shaping the viral membrane and contributes to the viral budding and release from infected cells. E protein is regarded as a possible therapeutic target due to its role in the pathogenesis of the virus [38].

Membrane Protein (M)

The membrane protein is a type III transmembrane glycoprotein with three transmembrane domains and short N-terminal and C-terminal regions inside the virus [29]. It works with the E, N, and S proteins and it is 222 amino acids long [42]. The membrane protein is critical for the assembly and morphogenesis of the viral particle [43] and RNA packaging [42]. It interacts with the nucleocapsid protein and the envelope protein to ensure proper incorporation of the viral RNA into the developing viral particle.

Nucleoprotein (N)

Viral RNA is packaged into ribonucleocapsids exclusively by the N protein [28]. Additionally, N protein promotes viral transcription and assists in virion formation [43, 44]. Because of its high immunogenicity, the N protein is a potential vaccine target [28]. The nucleocapsid protein is involved in viral RNA packaging, protecting the viral RNA from degradation, and maintaining the viral RNA's stability during replication and assembly. It also plays a role in modulating the host's immune response.

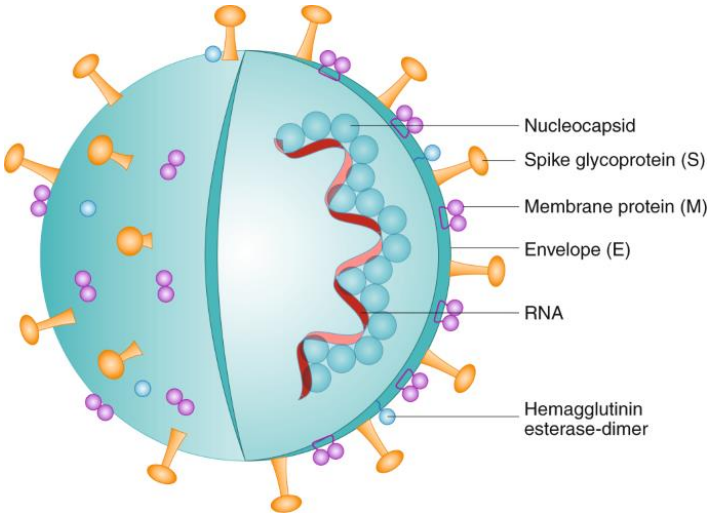

Figure 3: Structural Proteins of SARS-CoV-2 genome [45]

Nonstructural Proteins (NSPs) of SARS-CoV-2 genome

The sixteen nonstructural proteins (NSPs) of SARS-CoV-2 are encoded by genes located in the 5' region of the viral genome [28, 46, 47]. These NSPs are produced through a complex process of translation and proteolytic cleavage of two large polyproteins, pp1a and pp1ab, which are translated from the open reading frames (ORF1a and ORF1b) at the 5' end of the genome. The ORF1a and ORF1b overlap and are expressed as a single long polypeptide that is later processed into individual NSPs. The functions of these nonstructural proteins are vital for viral replication, transcription, and modulation of host immune responses [48, 49]. Here is a brief overview of the functions of the 16 nonstructural proteins of SARS-CoV-2:

Table 1: Table of SARS-CoV-2 NSPs functions

Protein	Role(s)	Reference
NSP1	Processes and facilitates RNA replication.	[50, 51, 52]
NSP2	Ties to prohibitins 1 (PHB1) and prohibitins 2 (PHB2).	[53, 54]
NSP3	It is reported to hasten mRNA transcript translation and impede host protein synthesis.	[55]
NSP4	Its primary function is replication and the synthesis of replicative structures.	[55]
NSP5	Involved in the replication mechanism of viral polyprotein	[56]
NSP6	Helps the host endoplasmic reticulum to initiate the formation of autophagosomes.	[56, 57]
NSP7	Creates a compound with NSP8 and NSP12 to produce NSP8's RNA polymerase activity.	[46. 51]
NSP8	Plays an active role in the activity of protease.	[58]
NSP9	Found to be involved in RNA replication and viral pathogenicity in a complex with NSP 8.	[50, 54]
NSP10	Performs a crucial part in the cap methylation of viral mRNAs.	[57]
NSP11	Vital for the viral RNA genome's transcription and replication.	[49]
NSP12	It's crucial in replication and transcription.	[49]
NSP13	Plays a vital role in the activity of RNA TPase and helicase.	[58]
NSP14	Essential for the action of the enzymes exoribonuclease and methyl transferase.	[45, 58]
NSP15	Activity of Mn(2+)-dependent endoribonucleases.	[57]
NSP16	Functions as Methyltransferase.	[28]

Variants of SARS-CoV-2

Viruses constantly change or mutate to produce new variants that occur over time [59]. Some of the new variants emerge and disappear whereas others persist [59]. Comparatively, RNA viruses have a higher mutation rate compared to DNA viruses. SARS-CoV-2 though is an RNA virus but have a less much mutation compared to the other RNA virus due to the possession of an enzyme that proofreads most of the errors that are made as the virus replicate in the host cell cytoplasm [60, 61, 62]. The variants occur when the strain undergoes mutation and expresses new phenotype as a result of natural selection.

Currently according to the WHO, there are four variants of concern; Alpha variant with scientific name of B.1.1.7 which was first identified in the United Kingdom, the Beta variant with scientific name B.1.351 which originated from South Africa, Gamma variant with scientific name P.1 which originated from Brazil and Delta strain with scientific name B.1.617.2 which originated from India [63, 64]. Another variant, Omicron strain with scientific name B.1.1.529 was reported to the WHO from samples collected from Botswana and South Africa. This variant was named and classified as variant of concern on November 26, 2021 [65]. There are currently two Variants of Interest, which are the Lambda variant and the Mu variant according to the WHO [59].

Alpha variant of SARS-CoV-2

The Alpha variant of SARS-CoV-2, also known as lineage B.1.1.7, is a variant of concern that was first identified in the United Kingdom in late 2020 [66]. This variant has been associated with increased transmissibility and has spread to many countries worldwide. The Alpha variant has demonstrated enhanced transmissibility compared to earlier strains of SARS-CoV-2 [67]. It spreads more easily from person to person, leading to higher case numbers and potentially faster rates of community transmission.

The Alpha variant carries several mutations, including mutations in the spike protein [68, 69]. One of the most significant mutations is N501Y, which affects the receptor-binding domain of the spike protein, potentially increasing its affinity for the ACE2 receptor on human cells. After its initial detection in the United Kingdom, the Alpha variant quickly spread to multiple countries across different continents. Its ability to transmit efficiently has contributed to its rapid global dissemination [70, 71]. Some studies have suggested that the Alpha variant may be associated with an increased risk of hospitalization and disease severity, although more research is needed to fully understand its impact on clinical outcomes [72, 73, 74].

While existing COVID-19 vaccines have shown effectiveness against the Alpha variant, some studies have indicated a slight reduction in vaccine efficacy, particularly after the first dose. However, vaccination remains crucial in reducing severe outcomes and preventing the spread of the virus [75].

Beta variant of SARS-CoV-2

The Beta variant of SARS-CoV-2, also known as lineage B.1.351, is another variant of concern that was first identified in South Africa in late 2020 [76]. Similar to the Alpha variant, the Beta variant has raised global attention due to its potential implications for transmission dynamics, disease severity, and vaccine effectiveness. The Beta variant carries multiple mutations in the spike protein, including E484K, K417N, and N501Y [77, 78]. These mutations are of particular concern as they may impact the virus's interaction with the human immune system and potentially affect vaccine efficacy [79, 80]. Studies have indicated that the Beta variant may partially escape the immune response induced by previous infection or vaccination, leading to reduced vaccine effectiveness against this variant [81]. However, existing vaccines still provide protection against severe disease and hospitalization, even if they may be somewhat less effective in preventing mild or moderate infections.

Since its first detection in South Africa, the Beta variant has been reported in multiple countries worldwide [82]. Its global presence underscores the importance of ongoing genomic surveillance to track its spread and understand its epidemiological significance [83]. Some evidence suggests that individuals previously infected with other variants may be at risk of reinfection with the Beta variant due to its genetic differences. This highlights the need for continued vigilance and research into the variant's behavior [84]. The impact of the Beta variant on disease severity is still being studied. While some studies have suggested that it may be associated with an increased risk of severe disease, more research is needed to fully understand its clinical implications [82, 84].

Gamma variant of SARS-CoV-2

The Gamma variant of SARS-CoV-2, also known as lineage P.1, is another variant of concern that was first identified in Brazil in late 2020 [85]. This variant has raised global attention due to its potential implications for transmission dynamics, disease severity, and vaccine effectiveness. The Gamma variant carries multiple mutations in the spike protein, including E484K, K417T, and N501Y [82, 86, 87]. These mutations are of particular concern as they may impact the virus's interaction with the human immune system and potentially affect vaccine efficacy [85, 87]. Some studies have suggested that the Gamma variant may be more transmissible than earlier strains of SARS-CoV-2 [88]. This increased transmissibility could contribute to higher case numbers and faster rates of community transmission. Since its first detection in Brazil, the Gamma variant has been reported in multiple countries worldwide [85]. Its global presence underscores the importance of ongoing genomic surveillance to track its spread and understand its epidemiological significance [81, 83, 85].

Like the Beta variant, the Gamma variant may also partially escape the immune response induced by previous infection or vaccination, leading to reduced vaccine effectiveness against this variant [87]. However, existing vaccines still provide protection against severe disease and hospitalization, even if they may be somewhat less effective in preventing mild or moderate infections [87, 88].

Delta variant of SARS-CoV-2

The Delta variant of SARS-CoV-2, also known as lineage B.1.617.2, is a highly transmissible variant that was first identified in India in late 2020 [89]. This variant has quickly become a variant of concern and has spread to numerous countries worldwide. The Delta variant is known for its significantly increased transmissibility compared to earlier strains of SARS-CoV-2. It is believed to be one of the primary drivers of recent surges in COVID-19 cases in many regions [88, 90]. The Delta variant carries multiple mutations in the spike protein, including L452R and T478K. These mutations have been associated with increased transmissibility and potentially enhanced infectivity [90]. Since its first detection in India, the Delta variant has rapidly spread to numerous countries across different continents [91, 92]. Its high transmissibility has contributed to its global dissemination. Studies have indicated that the Delta variant may have some level of reduced susceptibility to neutralization by antibodies, potentially affecting vaccine effectiveness [91]. However, existing vaccines still provide significant protection against severe disease, hospitalization, and death, even if they may be somewhat less effective in preventing mild or moderate infections [93].

Omicron variant of SARS-CoV-2

The Omicron variant of SARS-CoV-2, also known as lineage B.1.1.529, is a newly identified variant of concern [94, 94]. It was first detected in November 2021 in South Africa and has since been reported in multiple countries worldwide. High Number of Mutations: The Omicron variant has a substantial number of mutations in the spike protein and other regions of the viral genome. Some of these mutations have been associated with potential changes in the virus's behavior and properties [95, 96, 97].

The Omicron variant has quickly spread to various countries, leading to growing concerns about its potential impact on global health and public health measures [97]. Initial reports suggest that the Omicron variant may have increased transmissibility compared to other variants of SARS-CoV-2 [94, 98]. This could lead to faster rates of community transmission. There are concerns about the Omicron variant's potential impact on vaccine effectiveness.

Some mutations in the spike protein might affect the virus's ability to evade the immune response induced by previous infection or vaccination [97, 99]. However, more research is needed to fully understand the extent of vaccine evasion. The impact of the Omicron variant on disease severity is still being studied [96, 99]. It is essential to determine whether infection with this variant is associated with increased risk of severe disease compared to other strains of SARS-CoV-2 [100]. Given the emerging nature of the Omicron variant, continuous monitoring, and research efforts are critical to understand its spread and impact fully [84, 96, 99]. Public health authorities worldwide are closely monitoring its characteristics to guide effective response measures and adapt vaccination strategies to address its potential impact on global health [92, 94, 99, 100].

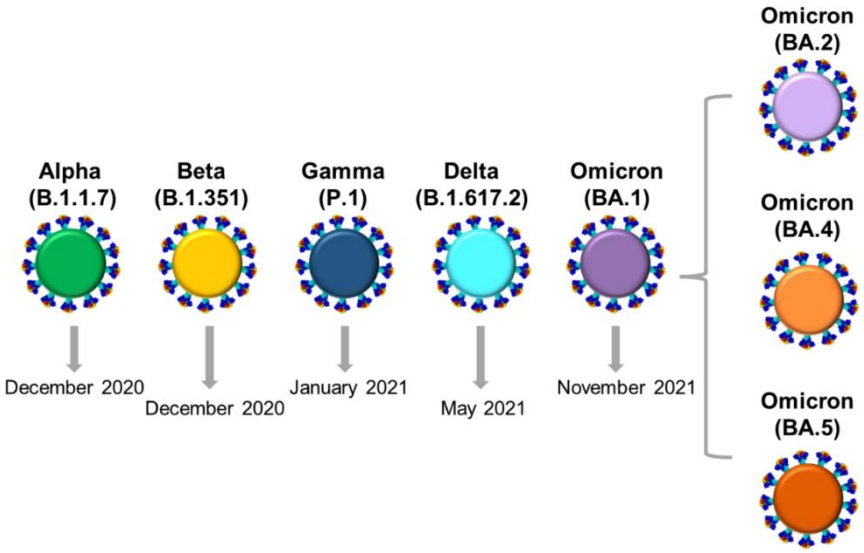

Figure 3: Variants of SARS-CoV-2 [101]

Pathogenesis of SARS-CoV-2

Evidence from genomic studies in Ghana and other countries has shed light on the relationship between specific genetic variants and disease severity. SARS-CoV-2 has affinity for epithelial and endothelial cells that expresses ACE-2 such as the type II alveolar cells, epithelial cells of the small intestines, lungs, hearts and kidneys [102]. ACE-2 on the epithelial cells of the lungs serves as the target receptor on the host cell of the receptor [103, 104].

After transmission, the S1 subunit of the spike protein binds to the ACE-2 on the host cell [104] and the fusion of the membrane is mediated by the S2 subunit [105, 106]. The complex formed between the ACE-2 and S protein undergoes proteolytic process, and this process is mediated by type II transmembrane serine protease (TMPRSS2) enzymes [107]. A cellular enzyme named *furin* located at S1/S2 site cleaves the S protein and this cleavage is important for the virus to enter into the lung cells [108].

After entry into the host cell, the virus uncoats and its genome is released into the cytosol of the host cell [108]. SARS-Cov-2 has a positive-sense genome, thereby producing its own genomes and proteins when attached to the host cell's ribosomes [106, 107, 108]. The +ssRNA functions as mRNA for orf1 and orf2 genes, which are then translated into polyproteins pp1a and pp1ab respectively [28, 81, 90].

The ppla and pplab undergoes proteolytic processing to yield the sixteen nonstructural proteins [84, 92], which also together proceeds to form the viral replicase complex [93]. The host cell's ribosomes translate the viral RNA into RNA polymerase proteins [100, 103]. The polymerase enzyme synthesizes negative-sense RNA strands which serves as template mRNA for translation into viral structural and accessory proteins E, M and S by the ribosomes in the host cell's endoplasmic reticulum [109, 110]. The ribosomes present freely in the cytosol translate viral protein N. The virion is then assembled at the Endoplasmic Reticulum – Golgi Intermediate Compartment (ERGIC), the progeny then exists the host cell by exocytosis where they spread and infect other cells [111, 112, 113].

The virus has mechanisms to subvert the immune response from the host and spreads from cell to cell causing injury [114, 115, 116]. Studies have indicated that papain-like protease (Plpro) was found to suppress interferon production, deregulates immune responses from monocytes and macrophages, and aids in the spread of the virus [117, 118]. Another study indicates that ORF8 protein down regulates MHC-1 and therefore prevents antigen presentation and T-cell activation [119, 120].

The entry of the virus into the host cell elicits inflammatory response by releasing cytokines, chemokines and other inflammatory cells resulting in cytokine storm which can lead to organ failure or damage in severe disease [119, 121].

The incubation period for the virus is 5-6 days on the average before the appearance of symptoms [117, 119, 120]. Majority of symptomatic patients shows symptoms on the average of 11.5days after infection [122]. Clinical presentations of COVID-19 include myalgia, fatigue, fever, dry cough, headache, sore throat and shortness of breath [122, 123]. Age, sex, underlying commodities such as diabetes, lung disease, cardiovascular disease, kidney disease and obesity have been reported to be associated with increased severity of the disease and admittance of patients to the intensive care unit (ICU) [124, 125].

Conclusion:

Understanding the genomic structure, genetic variants, and pathogenicity of SARS-CoV-2 is of paramount importance for an effective public health response to COVID-19. Continuous genomic surveillance, international collaboration, and ongoing research efforts are essential in addressing the challenges posed by the evolving nature of the virus and devising evidence-based strategies to combat the pandemic.

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