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SARS-CoV-2 Genes Mutations Are a Challenge behind Its High Contagiosity: A Review

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ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) has threatened global health security and raised a major international health concern. The new genetic background of this virus has existed due to mutations in either structural proteins, nonstructural proteins, or both. Spike glycoprotein recombination was presumed as a cause of cross-species transmission. To undertake a narrative review of the predisposing genetic variations and mutations of SARS-CoV-2, this is presumed to endorse its high contagiosity. Keyword search on a database of Medline-PubMed, Embase, and Science Direct was conducted. Relevant journals and bibliographies list of primary articles were screened manually. Relevant articles on novel Coronavirus 2 (nCoV-2) mutations were identified. This review revealed six main aspects of nCoV-2: high affinity to Angiotensin-Converting Enzyme 2 (ACE2) due to the variations of structural-proteins; high differentiation mechanisms could be attributable to the mutations of nonstructural-proteins; high diversity was speculated to the presence of one or more intermediate hosts; high novelty was attributed to its distinction to other SARS-CoV; and high mutagenicity as its noticed through comparing it to the first-case of Wuhan. Our narrative review revealed that SARS-CoV-2 is liable for multiple mutations, and its high contagiosity might be attributed to its mutation features. Hence, the prevention and controlling strategies of SARS-CoV-2 should be given more emphasis not only to its mutagenicity but also to the early detection of the viruses and provision of effective anti-viral agents.

Keywords: SARS-CoV-2, Coronavirus, Mutation, COVID-19, Spike protein, N501Y

INTRODUCTION

Wuhan, a Chinese city from which a highly contagious SARS-CoV-2 virus has transmitted worldwide, is raising a major international concern besides threatening global health security. That virus silhouettes like a spherical particle with a crown fringe, belong to the *Coronavirinae* genus, have a novel genome, and appear by the end of 2019 [1-3]. As a composition of its features, SARS-CoV-2 was given as a name for that highly transmissible virus. High transmissibility of nCoV-2 was noticed with a long incubation period before manifesting clinical symptoms like fever, dry cough, fatigue, and shortness of breath [4,5]. As of 9 April 2020, 436,198 plus million cases have been confirmed around the world with 85,522 deaths [6]. The basic reproductive number (R0) of nCoV-2 was estimated to be 1.4-2.5 based on the WHO-International Health Regulations Emergency Committee meeting on the nCoV-2 outbreak.

SARS-CoV-2 is a positive-sense RNA virus [7]. It belongs to the beta-coronavirus genus of the *Coronavirinae* subfamily in the family of *Coronaviridae*, as known as the largest RNA viruses with a genome size of 30 kb [1,2,4,5]. It has multiple structural and non-structural proteins. About two-third length of the SARS-CoV-2 whole-genome Open

Reading Frame (ORF1a and ORF1b) encode 16 Non-Structural Proteins (nsp1 to nsp16) [7]. Other ORFs encode the structural portions, which are the Nucleocapsid protein (N), the Membrane protein (M), the Envelope protein (E), and the Spike protein (S) [8]. These four proteins are essential to assemble the virion and pathogenicity of nCoV-2 virus. Attachment to the host cell is the responsibility of the virus' S-proteins. Shaping the virion, endorsing the membrane curvature, and binding to the nucleocapsid are M-protein responsibilities. While the key roles of the E-protein are the virus pathogenicity and assembly, binding the RNA genome to different mechanisms is the key role of the N-protein [7].

SARS-CoV-2 is phylogenetically close to SARS-CoV [8,9]. Commonly, genetic diversity arises from mutation and recombination [10]. Genetic novelty is only obtained by a mutation in which one-base of nucleotide is replaced with another or a nucleotide added or deleted [11]. Genetic diversity, however, increases by recombination where new genetic backgrounds exist by mutations [12,13]. These sources of genetic diversity had been proved for SARS-CoV-2 [11]. Studies were assumed the cross-species transmission may boost through spike glycoprotein recombination [14,15]. The identical genomic sequence of SARS-CoV-2 was proved from paired-infected individuals sharing the same shelter. However, substantial minority variations were detected for deep sequencing of viral genomes within different individuals. This pattern of minority variations, which are predisposed to mutations, might reappear during the continuous spreading of SARS-CoV-2 [16]. Therefore, this review was conducted to illustrate the genetic variation of SARS-CoV-2, which was presumed to endorse epidemic spread.

METHODS

A systematic search on the database of Medline-PubMed, Embase, and Science Direct was conducted to review relevant articles using "COVID-19", "SARS-CoV-2", "mutation", and "genome" as keywords. Manual search on some journals and websites like the WHO-COVID database was carried out as well. To maximize our search sensitivity, the reference list of the identified articles in the initial search was examined for further relevant studies. The included articles were identified with the genetic mutation of SARS-CoV-2. The focus period of the search was from December 1st, 2019 to March 31st, 2020 because during this period the SARS-CoV-2 has a global concern for its high contagiosity.

RESULTS AND DISCUSSION

Relevant articles were included in our review and identified into two broad categories based on their mutation types. Most of the included articles were concentrated on structural-proteins mutations, while the rest were focused on mutations other than the structural ones. Characteristics of the studies included in this review were explained in Table 1, in which the source of sequence analysis and the sequence alignment were elucidated. Moreover, the review showed several mutations exist in SARS-CoV-2 that increases its high contagiosity and transmissibility. Those mutations were presented in Table 2 based on each included article. Summary of the results from all included studies in this review was revealed accordingly as followed:

Table 1 Summary of study characteristics: source of sequence analysis and sequence alignment

References	Title of article	Country	Source of retrieving of sequence analysis	Method of genomic sequence alignment	Constructed of Phylogenetic tree
[17]	Role Of Changes In SARS-Cov-2 Spike Protein In The Interaction With The Human Ace2 Receptor: An In Silico Analysis	Venezuela and USA	GenBank	SWISSMODEL (Deep View/Swiss-PdbViewer 4.01)	Poisson Correction MEGA
[18]	Complete Genome Sequence of a 2019 Novel Coronavirus (SARS-CoV-2) Strain Isolated in Nepal	Nepal	GISAID; strain identifier EPI_ ISL_405839) and NCBI BLAST	CLUSTAL W	MEGA 10.0.5.
[9]	COVID-2019:The role of the nsp2 and nsp3 in its pathogenesis	Italy	GISAID and GenBank	Fast Fourier Transform Online Tool and Bioedit v7.0.5	-

[19]	The 2019-new coronavirus epidemic: Evidence for virus evolution	Italy	GISAID and GenBank	multiple sequence alignment online and Bioedit v7,0,5	ML phylogenetic tree
[20]	The establishment of the reference sequence for SARS-CoV-2 and variation analysis	China	GISAID and NCBI BLAST	MEGA software (7.0.14)	ClustalW program of the MEGA software (7.0.14)
[16]	On the origin and continuing evolution of SARS-CoV-2	China	GISAID, GenBank, and NMDC	MUSCLE v3.8.31	the neighbor-joining method in MEGA-x
[11]	Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding	China	GenBank	Mafft software (version 7.450)	RAxML software (version 8.2.9)
[14]	Genotyping coronavirus SARS-CoV-2: methods and implications	USA	GISAID and GenBank	MSA tool Clustal Omega using the default parameters	-
[21]	The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2	Netherland and other countries	GenBank	multiple sequence alignments (MSAs)	IQ-TREE v.1.6.1
[22]	Using the spike protein feature to predict infection risk and monitor the evolutionary dynamic of coronavirus	China	Database of China National Genomics Data Center (NGDC)	used three encoding algorithms multidimensional scaling method in R	-
[23]	Fusion mechanism of 2019-nCoV and fusion inhibitors targeting HR1 domain in spike protein	China	-	Amino acid (aa) sequence alignment	-
[24]	Virus Isolation from the First Patient with SARS-CoV-2 in Korea	Korea	NCBI and GISAID	multiple-sequence aligned using MAFFT (v7.450)	MAFFT (v7.450)
[25]	Genomic Analysis of a 2019-nCoV Strain in the First COVID-19 Patient Found in Hangzhou, Zhejiang, China	China	NCBI and GenBank	Mafft	RAxML
[26]	Full-genome evolutionary analysis of the novel coronavirus (2019-nCoV) rejects the hypothesis of emergence as a result of a recent recombination event	Greece	NCBI nucleotide sequence Database and GISAID	MAFFT v7.4.2. and MEGA v1.0	RDP4 and Simplot v3.5.1

Table 2 Summary of study characteristics: CoV-2 genetic mutations

References	Title of article	Country	Name of the mutant gene	Notes
[17]	Role of Changes in Sars-Cov-2 Spike Protein in The Interaction With The Human ACE2 Receptor: An in Silico Analysis	Venezuela & USA	Spike protein: - (RBD) L455, F486, Q493, and N501. - Residues presents in capping loops V445, Y449, Y473, Q474, A475, E484, G485, F486, and N487. - longer capping loops	- The residues in SARS-CoV-2: N479 correspond to Q493 and T487 correspond to N501 (mutation from Civet to human). - Those mutations increase the affinity of the virus to nhACE2 receptors and its high virulence too.

[18]	Complete Genome Sequence of a 2019 Novel Coronavirus (SARS-CoV-2) Strain Isolated in Nepal	Nepal	- C24019T: silent mutation at the spike gene (codon AAC to AAT). - T8782C: silent mutation in ORF1a (codons AGT to AGC). - T9561C: non-silent mutation in ORF1a (codons TTA to TCA,) - C15607T: silent mutation in ORF1b (codons CTA to TTA,) - C28144T: non-silent mutation in ORF8b (codons TCA to TTA) - T29095C: silent mutation in nucleocapsid (codons TTT to TTC)	
[9]	COVID-2019:The role of the nsp2 and nsp3 in its pathogenesis	Italy	- Stabilizing mutation in nsp2 - Destabilizing mutation in nsp3	Stabilizing mutation of the nsp2 protein could account for CoV-2 high contagiosity, while the Destabilizing mutation in nsp3 proteins could suggest a potential mechanism differentiating CoV-2 from SARS
[19]	The 2019 new coronavirus epidemic: Evidence for virus evolution	Italy	- Spike Glycoprotein - Nucleocapsid protein.	536th AA and 644th AA positions in CoV-2 have an asparagine residue and a threonine residue, respectively, instead of a serine residue in bat SARS.
[20]	The establishment of the reference sequence for SARS-CoV-2 and variation analysis	China	- ORF 1a (nt8782), - ORF 8 (nt28144) - N region (nt29095) in 28, 29, and 11 strains	Mutation occurs in ≥3, these are the most important locations
[26]	Full-genome evolutionary analysis of the novel coronavirus (2019-nCoV) rejects the hypothesis of emergence as a result of a recent recombination event	Greece	- ORF1a	Discordant phylogenetic relationships between CoV-2 and RaTG13 clade with their closest partners, the Bat_SARS-like coronavirus sequences.
[16]	On the origin and continuing evolution of SARS-CoV-2	China	- T8517C: synonymous mutation in ORF1ab (codon AGT to AGC). Non-synonymous mutation in: - ORF1ab (A117T, I1607V, L3606F, I6075T), ORF3a (G251V), ORF7a (P34S), ORF8 (V62L, S84L). - S (H49Y, V367F) - N (S194L, S202N, P344S)	- A total of 149 sites mutations across the 103 sequenced strains - Nonsynonymous mutation had derived alleles in at least two SARS-CoV-2 strains
[11]	Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding	China	- Spike protein (longer spike protein encoded compare to other CoV-viruses)	As it's compared to bat-SL-CoVZC45 and bat-SL-CoVZXC21
[14]	Genotyping coronavirus SARS-CoV-2: methods and implications	USA	Spike protein, Nucleoprotein, RNA polymerase, and RNA primase.	Those are the major mutations, and many SPNs mutations were detected as well

[21]	The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2	Netherland and other countries	- ORF1a - ORF1b	- Indicated a gap between SARS-COV &SARS-COV-2
[22]	Using the spike protein feature to predict infection risk and monitor the evolutionary dynamic of coronavirus	China	- Spike protein	An extra cleavage (furin site b/nS1 & S2(R682-R683-A684-R685) make it unique from other CoVs
[23]	Fusion mechanism of 2019-nCoV and fusion inhibitors targeting HR1 domain in spike protein	China	- Spike proteins (the HR1 of S2 subunits had 8 mutation regions)	HR1 was used as a target site for making the 6-HB complex, which helps in inhibiting the entrance of the CoV-2 to hACE2.
[24]	Virus Isolation from the First Patient with SARS-CoV-2 in Korea	Korea	- Spike gene - ORF1ab, ORF3a - E gene	9 mutations were identified comparing the one found in Wuhan china; from them, six have changes in amino acids.
[25]	Genomic Analysis of a 2019-nCoV Strain in the First COVID-19 Patient Found in Hangzhou, Zhejiang, China	China	-Spike gene	- Out of 29 strains from China, the USA, Japan, and Finland, some SNPs were identified. - A synonymous mutation at loci 8782 (T/C and C/T) - A nonsynonymous mutation at loci 28144 (tyrosine-> histidine).

Structural Proteins Mutations

The structural proteins possess much higher immunogenicity for T-cell responses than the non-structural proteins [27]. Specifically, spike-protein is an important determinant of SARS-CoV-2 pathogenicity and host range [28,29]. A mutation of S-protein (23403A>>G) has been suggested to have a high affinity to ACE2 [14]. A genetic variation in S-gene was detected by present cytosine instead of guanine at position 22224 and tryptophan instead of serine as an amino acid alteration [24]. Several Amino Acids (AA) substitutions and deletions in Receptor Binding Domain (RBD) were detected in SARS-CoV-2; besides, residues present in the capping loops of SARS-CoV-2 (V445, Y449, Y473, Q474, A475, E484, G485, F486, and N487) were different as compared to that of SARS-CoV [17]. Spike glycoprotein- Heptad Repeated Region ½ (S-HR1/S-HR2) of the SARS-CoV-2 were mediating the fusion of the virus to ACE2 [23]. Xia and his colleagues revealed the presence of 8 mutations of the 21 residues in the HR1 core regions of S2-subunits of the spike proteins. Although the mutation presented in this region, the fusion inhibitors of SARS-CoV-2 used HR1 as the target sites for making a Six-Helix Bundle (6-HB) complex; which inhibits CoV-2 entrance to the hACE2 [23]. Furthermore, a study found a silent mutation at S-gene where codon AAC was substituted by AAT [18].

In the SARS-CoV-2 strains found in the US, the Nucleocapsid (N) protein-gene had three mutations (28881G>>A, 28882G>>A, and 28883G>>C) [14]. Another study disclosed a silent mutation at the nucleocapsid gene (codon TTC instead of TTT) [18]. Additionally, S-protein (H49Y, V367F) and N-protein (S194L, S202N, P344S) had derived alleles as non-synonymous mutations in at least two strains of CoV-2 [16]. The other two mutations were detected in Envelope-gene (E) of CoV-2, thymine substituted adenine at 26354 positions, while a histidine amino acid present instead of leucine at 7609 positions [24]. Altogether, the genes encoding the RNA polymerase, spike proteins, and nucleoproteins, were subjected to repeated mutations [14]. Likewise, residues of CoV-2 at S-protein (Asn439, Asn501, Gln493, Gly485, and Phe486) have found variable in RBD and they were responsible for the binding to the ACE2 [14].

Non-structural Protein Mutations

Open Reading Frames (ORF1a and ORF1b) are representing about two-thirds length of the nCoV-2 whole genome. This part of the virus encodes 16 Non-structural Proteins (nsp1 to nsp16) [7]. Numerous studies found mutations in Nonstructural Proteins (nsps), especially nsp2 and nsp3 [9,18,20,26]. Angeletti and her colleagues demonstrated in their study that there are alterations in 11 residues of nsp2 and 46 residues of nsp3 of nCOV-2 as compared to bat

coronavirus [9]. Referring to the amino acids, a serine substitutes a glycine residue in position 723, while in position 1010 a proline residue substitutes isoleucine of nCOV-2 had been detected as well [9]. Likewise, the silent mutation has been found in T8782C of the ORF1a where codons AGC substitutes AGT, while codons TTA encodes instead of CTA at the C15607T of ORF1b. On the other hand, changing codons TTA to TCA of T9561C in ORF1a and codons TCA to TTA of C28144T in ORF8b were detected as non-silent mutations [18]. Another study found several non-synonymous mutations that affected four nonstructural proteins. All those proteins had derived alleles in more than two CoV-2 strains, where those Single Nucleotide Polymorphisms (SNPs) as followed: A117T, I1607V, L3606F, and I6075T of ORF1ab; P34S of ORF3a; G251V of ORF7a; V62L and S84L of ORF8 [16].

Interestingly, a study had classified nCoV-2 into two major types based on the SNPs mutations in nonstructural proteins as 103 complete genome sequences were set as a comparison. A synonymous mutation at loci 8782 of the ORF1ab: T8517C and a non-synonymous mutation at loci 28144 of the nsp8: C251T and S84L were identified. Based on the latter, a major type "L" was defined due to the exhibition of "CT" haplotype in 72 strains out of 101 as T28144 localizes in the codon of Leucine; whilst 29 strains exhibited "TC" haplotype as C28144 localizes in the codon of Serine and this type was defined as a minor type "S". Authors suggested the "L" type is more aggressive than the "S" type due to its high transmissibility and replications [14,16].

Many SNPs mutations were detected in nsp8-gene (RNA primase protein: 28883G>>C, 28882G>>A, 28881G>>A, and 28144T>>C) as were identified by Yin's study. Other two non-synonymous mutations, as they were suggested to be critical for RNA replication, have been identified in nsp3 protein as well (241C>>T, 14408C>>T). A study proposed that replications of RNA virus could be highly improved with mutations in RNA primase and polymerase [14].

Altogether, a probable mechanism differentiation of nCoV-2 to SARS would be accounted for the destabilizing mutation in nsp3; however, nCoV-2 high contagiosity could be attributed to the stabilizing mutation in the nsp2 [9].

Intermediate Host of SARS-CoV-2

Numerous studies showed that bats were the source (nature host) of the nCoV-2 due to sharing 96% similarity of genomic sequencing [8,9,11,16,25,26]. On the other hand, researchers had struggled to detect the intermediate host of nCoV-2 [11,17, 21]. A study suggested that snakes were the intermediate host due to their Relative Synonymous Codon Usage (RSCU- bias) compared to other animals [15]. Another study proposed two candidates' reservoirs of nCoV-2: minks and bats due to their analogous infectivity pattern to nCoV-2 [8]. Another study revealed that Pangolins were the intermediate host of nCoV-2 as the authors had found a 99% of genetic similarity [17]. Remarkably, Tang, et al. suggested that neutral evolving sites should be considered rather than the diversity of nucleotides sequencing when tracing the intermediate host of nCoV-2. Besides, they had proved that genomic average was analogous between humans and Pangolins (ds=0.475) as it is between mice and humans (ds=0.5) [16]. In summary, many researchers speculated that nCoV-2 had jumped from bat to human through one or more intermediate hosts. They have recommended further studies to be concerted on detecting the intermediate host of nCoV-2 [20,25,30].

Novel SARS-CoV-2 Compared to the Previously Recognized SARS-CoVs

Attributable to the rapid escalation in the prevalence and incidence rates of SARS-CoV-2, it is domineering to be compared to the previously recognized coronaviruses [31,32]. Our review revealed that there were several amino acid substitutions and deletions in the S1 subunits Receptor Binding Domain (RBD) of the different spike protein of Bat-CoV and SARS-CoV compared to that of SARS-CoV-2; even with 97.7% of their whole spike proteins genome sequences were identical [17]. A study also revealed that five of the six critical amino acid residues in RBD were different between SARS-CoV-2 and SARS-CoV [16]. The substitutions of N479>>Q493, and T487>>N501 residue in SARS-CoV-2 increase its affinity to human ACE2 receptors compared to that of SARS-CoV. The two capping loops in the binding domain, which produce an increase in the electrostatic interactions between the spike protein and ACE2 receptor, were only present in human CoV (SARS-CoV and SARS-CoV-2); whilst they were absent from that of Bat-CoV [17]. Residues present in the capping loops of SARS-CoV & SARS-CoV-2, which had direct interaction with the ACE2, were different; R426, S432, T433, Y436, P462, D463, S472, and N473 for SARS-CoV; and V445, Y449, Y473, Q474, A475, E484, G485, F486, and N487for nCoV-2 [17]. Besides, the presence of the longer capping loops in SARS-CoV-2 increases its binding affinity to the receptors than that of SARS-CoV, Middle-East Respiratory Syndrome Coronavirus (MERS-CoV), and bat-SARS like-CoV (SL-CoVZXC21 and SL-CoVZC45) [11,16,17].

Lu, et al. studied the five gene-regions (E, M, 7, N, and 14) sequences of SARS-CoV-2 and bat-SARS-like-CoV; more than 90% similarity was identified [11]. However, their similarity with that of SARS-CoV and MERS-CoV were the

lowest, about 79% and 50% respectively. The coding region of the novel SARS-CoV-2 was similar to that of SARS-CoV and bat-SARS-like-CoV [11].

Furthermore, the Spike (S) gene of the SARS-CoV-2 exhibits the lowest sequence identity with that of bat-SL-CoVZXC21 and bat-SL-CoVZC45 [11,16,25]. Two studies indicated that there were several amino acid deletions at 455-457, 463-464, and 485-497 positions of the s1 C-terminal domain of bat-SARS like-CoV but not of SARS-CoV-2. Besides, the phylogeny of the complete RNA-dependent RNA polymerase (RdRp) gene of the SARS-COV-2 was different from SARS-CoV, indicating its novelty [11,14]. Although the SARS-CoV-2 and bat-SARS-likes CoV had high similarity in genome sequences, the phylogenetic relationships between SARS-CoV-2 and the Bat-SARS-like coronavirus sequences are discordant clustering [26]. Benvenuto, et al. demonstrated that SARS-CoV-2 and bat-SARS-likes CoV share the same amino acid sequences, except, the differences at two positions in the SARS-CoV-2 spike glycoprotein: 536th (asparagine residue) and 644th (threonine residue) instead of a glutamine and serine residue, respectively [19].

Next-Generation Sequencing Compared to Reference Genome of Wuhan

Despite to what extent the novel SARS-CoV-2 is mutagenic, the next-generation sequencing comparison with that of the Wuhan first SARS-CoV-2 case genome sequencing was considered. Lu and colleagues showed that although a 99.98% sequence identity of the whole genome sequence of eight cases; four non-synonymous mutations at positions (6943: C>>A,11739: T>>A, 28120: T>>C, and 27469: C>>T) were observed [11]. As compared to the first-case genome sequence of Wuhan, nine mutations were found in genome sequencing of the 1st-case in Korea (Five variants were found in ORF1ab, one variant in S gene, two variants in ORF3a, and one variant in E gene) [24]. Likewise, the 1st-case isolated in Nepal, indicated three silent mutations: (T8782C in ORF1a: codons AGT to AGC; C15607T in ORF1b: codons CTA to TTA, and T29095C in nucleocapsid: codons TTT to TTC), and two non-silent mutations: (T9561C in ORF1a: codons TTA to TCA and C28144T in ORF8b: codons TCA to TTA) [18].

A comparison of 95 full-length genomic sequences of SARS-CoV-2 strains from different countries, identified 13 variations sites in 1a, 1b, S, 3a, M, 8, and N regions; of which positions nt28144 in ORF8 and nt8782 in ORF1a showed a higher mutation rate among SARS-CoV-2 strains [20]. Hua and his colleagues identified SNPs in some strains out of 29 strains from China, the USA, Australia, Japan, and Finland [25]. A synonymous mutation at loci 8782 (T/C and C/T) and non-synonymous mutation at loci 28144 (tyrosine- >histidine) exist in china and the USA [26]. A recent genome sequence of 442 SARS-CoV-2 strains from the Global Initiative on Sharing All Influenza Data (GISAID) database revealed three mutations (28881G>A, 28882G>A, and 28883G>C) in the nucleocapsid protein-gene of the SARS-CoV-2 strains of USA [14].

The mutagenicity of SARS-CoV-2 is notably increasing among strains; a study reported 149 mutations sites (43 synonymous mutations (T8517C; in ORF1ab (codon AGT to AGC) and 83 non-synonymous mutations (ORF1ab (A117T, I1607V, L3606F, I6075T), S (H49Y, V367F), ORF3a (G251V), ORF7a (P34S), ORF8 (V62L, S84L), N (S194L, S202N, P344S) across 103 SARS-CoV-2 strains sequences. It also indicated that non-synonymous mutations had derived alleles in at least two SARS-CoV-2 strains [16].

At the end of 2020, a new variant of SARS-CoV-2 (N501Y) was detected in England, with rapid transmissibility, even as the rest of the country was managing to limit the spread [33]. The emerging N501Y mutation (an asparagine to tyrosine amino acid substitution at position 501 in the viral S gene) is becoming one of the major challenges of SARS-CoV-2 control [34]. SARS-CoV-2 has acquired 17 mutations, all at once, leads to amino acid changes in its proteins. Of them, 8 mutations were encoded in the spike protein, as N501Y was of the serious mutation that results in trouble of controlling the virus [33]. The N501Y mutation has been shown to increase the spike binding to the ACE2 receptor, which elevated its transmissibility [35,36]. It has been estimated that 52% of the increase of infectivity was due to N501Y substitution [34]. It is still a matter of speculation whether this mutation has arisen from an immune-compromised host or through an animal source [37]. Further investigations are ongoing on this virus and more intriguing questions regarding the newly mutated virus need to be answered.

Detection and Control of SARS-COV-2

Different technologies were used to verify SARS-COV-2 infection; polarimetric microscopy analysis was one of the methods used for the differentiation of viral infected and uninfected cells at an early stage [38]. Moreover, the SARS-CoV-2 serology Enzyme-Linked Immunosorbent Assay (ELISA) kit was also used for the detection of SARS-COV-2 infection at the early stage of the disease and provide the clue for taking appropriate measure for controlling

the spread of the infection [39]. Drone technology was also another opportunity proposed to combat SARS-COV-2 without human intervention [40]. The drone with thermal screening and day vision camera was an artificial intelligence technology that can detect the infected person without any human intervention [40]. It was also helpful for screening of SARS-CoV-2 in a highly-populated area like an institution, restaurant, and market places where the population is highly condensed [40].

Besides, the appropriate and effective usage of the antiviral agent can reduce the transmission of SARS-COV-2 [41]. There are two categories of antiviral agents: Direct-Acting Antiviral (DAA) and Indirect Acting Antiviral (IAA) [41]. The DAAs are directly targeted to specific viral components, like viral polymerase, or steps in the viral life cycle, without affecting other host cellular activities, however, it has a potential risk of drug-resistant mutations [39,42-44]. On the other hand, IAAs target host proviral factors and indirectly inhibit viral infection or replication. IAAs are not prone to viral mutations but they can alter the host cellular system and are not considered to be safe [41]. As a result, DAAs that targeting viral entry, proteases, and replication can serve as effective antiviral agents [41]. A combination of repurposed drugs can reduce the time, cost of treatment, and risk of drug-resistance, and increase therapeutic efficacy to facilitate progression into clinical trials [45]. However, a recent study shows that SARS-COV-2 is resistant to the commonest repurposed drug (Remdesivir) due to its drug-resistant mutation [46-48].

CONCLUSION

Our narrative review revealed that SARS-CoV-2 is liable for multiple mutations, and its high contagiosity might be attributed to its mutation features. This review exposed five main conclusions:

- Residues of CoV-2 at spike proteins were found variable in RBD, which were attributable to the high affinity to bind to the ACE2
- A probable mechanism differentiation of nCoV-2 to SARS would be accounted to the destabilizing mutation in nsp3; however, nCoV-2 high contagiosity could be attributed to the stabilizing mutation in the nsp2
- Speculation presumed that nCoV-2 had jumped from bat to human through one or more intermediate hosts
- SARS-CoV-2 has different spike proteins and longer capping loops, which increases its affinity to hACE2 receptors as compared to SARS-CoV and MERS-CoV
- The mutagenicity of SARS-CoV-2 was notably increasing among strains as illustrated across 103 SARS-CoV-2 strains sequences

These are the foremost conclusions that were driven from the reviewed articles. Based on the results of the included articles, strategies aimed to control and prevent SARS-CoV-2 should be given more emphasis not only to its mutagenicity but also to the early detection of the viruses and provision of effective anti-viral agents.

DECLARATIONS

Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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