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Review Article

Comparing Genetic Information of Severe Acute Respiratory Syndrome Corona Virus 2 and SARS CoV and Middle East Respiratory Syndrome Corona Viruses; A Review Study

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Abstract

Background & Objective: The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a global infection and a continuing pandemic. Symptoms have been associated with age, biological sex, and other previous present health situations.

The aim of this study was to make a genetic comparison between the SARS-CoV-2, SARS-CoV, and Middle East Respiratory Syndrome (MERS)-CoV using phylogenetic methods.

Materials & Methods: In this review study, previously published papers were collected from 2010 to 2020 using electronic sources in reliable databases such as Scopus, PubMed, ISI, Google Scholar, and Science Direct. Then, we performed the bioinformatics study. For sequences alignment, analysis, and phylogenetic construction, all sequences from SARS-CoV-2, SARS-CoV, and MERS-CoV were obtained from the GeneBank database.

Results: Eighty percent of SARS-CoV and 50% of MERS-CoV RNA sequences shared with SARS-CoV-2 RNA and SARS-CoV-2 show additional genomic regions. The phylogenetic analysis of the full-length genome sequence shows that SARS-CoV-2 has the highest similarity with SARS-CoV, but it has a lower similarity with MERS-CoV. Considering the close relationship between SARS-2 and SARS, the examination of the amino-corrosive translocation of completely different proteins may prove that there are fundamental and utilitarian differences between SARS-2 and SARS.

Conclusion: Although COVID-19 pathogenicity is not well known, MERS-CoV and SARS-CoV pathogenesis still can be the best source of COVID-19 information. The global effect of this new epidemic is yet uncertain. So, analyzing genome sequencing is important for epidemiological, clinical, and experimental studies.

Keywords: Coronavirus genome, MERS-CoV, SARS-CoV, SARS-CoV-2, Phylogenic tree, COVID-19

Introduction

In late December 2019, it was observed that many people in Wuhan, China, were suffering from SARS-like pneumonia, which was later dubbed COVID-19 (SARS-CoV-2) by the World Health Organization (WHO) (1).

The world's first coronavirus practice in China for 2002–2003 resulted in 8098 cases and 774 deaths from Severe Acute Respiratory Syndrome (SARS) and in 2465 cases in 2011, Middle East Respiratory Syndrome (MERS) (2). Coronavirus newly identified from zoonotic origin was the relevant cause of both cases including SARS-CoV and MERS-CoV (3, 4). Human-to-human communication has an impact on people as a

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result of close contact (5-7). Seven types of coronavirus can infect people all over the world, but most people are infected with these four types of coronavirus: 229E, NL63, OC43, and HKU1. Usually, they cause respiratory infections and are commonly resistant to severe diseases like MERS and SARS, while COVID-19 causes infectious conditions (8).

The CoVs are classified into Nidovirales orders, Coronaviridae families, and Coronavirinae subfamilies, with four genera: α-coronavirus, β-coronavirus, γ-coronavirus, and δ-coronavirus (8, 9). CoVs are host-specific and are known to infect humans as well as several other vertebrates including mammals and birds. High mutation and recombination rates may allow the spread of coronaviruses across species (10).

The alpha and beta viruses include all known and most important coronaviruses, infecting humans. Bats can be infected by both alpha and beta coronavirus and can also infect other species, including people, camels and rabbits. The zoonotic coronavirus pool can spread widely in the environment and cause other sensitive species infection. A storage facility may be multiple times infected (11, 12). SARS-CoV is of the Coronaviridae family, Nidovirales order, β-coronavirus genus, B lineage, even though it was the first member of β-coronavirus lineage C to be found as a novel coronavirus, MERS-CoV was in a similar family, order and genus as SARS-CoV. In contrast, SARS-CoV-2, in the same family and genus as MERS-CoV and SARS-CoV, and the genomic research found that SARS-CoV and SARS-CoV-2 have a greater similarity. It was identified as a lineage B member by scientists (11, 13-15). Since the Covid 19 disease has not yet been specifically treated, comparing genetic information and similarities and differences with SARS and MERS can help researchers design targeted therapies.

As a result, we intend to provide a brief overview of the frontier knowledge and provide updates on the primary features of SARS-CoV-2, MERS-CoV, and SARS-CoV, and in contexts of an animal host and genome organization, in response to COVID-19 infection. Genetic information about these three viruses and the differences that exist can lead to advances in understanding the challenges of pathogenesis, treatment, and prevention in the future.

Host

The interactions between animals and human, especially SARS-CoV-2, and SARS-CoV on the wetland market in China, should be noted for these human coronavirus (hCoV) outbreaks. In view of the early SARS patients being related by SARS-CoV to the Guangdong wildlife market, the product is supposed to be made of wild animals sold on these markets (counting palm calves). The following was the isolation from palm civet in the wild animal market of CoV strains (99.8%) with high SARs-CoV homology. The CoV derived from palm civet can therefore be thought to switch between them. In addition, some SARS patients (75%) have a clear history of contact with palm civets during a sporadic occurrence in Guangdong, which supports the previous epidemiological hypothesis that palm c is an important SARS-CoV host animal. Therefore, there is a reason to believe that based on this strong evidence, palm civets are important intermediate hosts of SARS-CoV (16-18). The SARS-like-COV strain, with its 88-92% genomic identity to CoV from human beings and civil cats, was removed from Chinese horseshoe bats, clearly indicating bats to be natural SARS-CoV hosts.

MERS-CoV is supposed to come from bats as well. The RNA fragment obtained by PCR amplification of nucleic acid isolated from shows the bats to be the source of MERS-CoV and was 100 percent of the nuclotide identity of MERS-CoV. The ability to replace bats with no symptoms in MERS patients has been demonstrated, suggesting that bats are the ideal MERS-CoV reservoirs. The indirect role of MERS-CoV dromedary camels reserves is supported by much evidence (16, 19, 20). Two virological studies have shown MERS-CoV circulating in dromedaries and have shown that they can potentially be cross-infected by human

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beings and MERS CoVs high genomic identity is recorded consecutively (99.2–99.5%) which is separated from the dromedary and the human (16, 21, 22).

Later, several serological studies complete the storage possibilities of dromedaries and the natural human-to-human transmission. The origins of SARS-CoV-2 are more complicated. SARS-CoV-2, like SARSCoV, is thought to be associated with commercial activities in the Wuhan wet market. SARS-CoV-2 and BatCoV RaTG13 (bat-CoV) were discovered to be genetically similar, leading researchers to believe that bats could be a natural reservoir of SARS-CoV-2. Additional research has revealed that the SARS-CoV-2 and pangolin-CoV genomes are very similar, which are isolated from pangolin (16).

The host is given to people, causing the spread from person to person. Compared to MERS and SARS, COVID-19 is thought to be zoonotic contamination transmitted from creatures to people, at that point taken after by a quick human to the human transmission that causes extreme respiratory contaminations and significant mortality. It is considered that bats have distinguished infections starting in this species as the potential vector to human contaminations. Furthermore, as bats live in colonies, they show a chance of transmitting the infections evenly (intra-species) which contributes to the vertical (cross-species) spreading capacity. The two exceedingly pathogenic strains of CoVs; MERS-CoV, and SARS-CoV were recognized both in bat species and in creatures included in transmission to people. It is worthy to note that the primary exceedingly pathogenic strain of coronavirus, SARS-CoV-1, includes a moo hereditary similitude with other known coronaviruses (39% with bovine coronavirus and 46% with porcine scourge loose bowels virus). Also, three comparisons were made with coronavirus strains from pangolins. The primary (February 18, 2020) compared the arrangements of COVID-19 with the coronaviruses in illicitly trafficked pangolins to appear a grouping likeness between 85.5 and 92.4%, with the ensuing papers (February 20, 2020), detailing arrangement likenesses with pangolin coronaviruses at 90.23% and 91.02%, separately (23). MERS-CoV circulates widely in dromedary camels as a result of zoonotic transmission of the infection. MERS-CoV and SARS-CoV are primarily transmitted from person to person via nosocomial (hospital-acquired) transmission (24).

Civets were considered as intermediate hosts and bats as natural hosts for SARS-CoV (8). MERS-CoV was most probably extended at least 30 years ago from bats to dromedary camels, and has been prevailing in dromedary camels since then (25).

Materials & Methods

This paper is a scoping review study and bioinformatics analysis. We have looked for keywords such as MERS-CoV, SARS-CoV, and SARS-CoV-2, and genome from 2010 to 2020, in e-databases like PubMed, Scopus, Google Scholar, ISI, and Science Direct. For the bioinformatics study, we obtained all sequences (the amino acid and coding sequences) of MERS-CoV, SARS-CoV, and SARS-CoV-2 from GeneBank database (https://www.ncbi.nlm.nih.gov/genbank/), and their accession numbers were used to draw the phylogenetic tree. The sequence alignment of 3 human Coronavirus genomes and polyprotein ORF1ab, spike (S), membrane (M), envelope (E), and nucleocapsid (N) sequences was performed using CLUSTALW.

Results

Genomic information of Coronaviruses

Coronaviruses (CoVs) are the enveloped RNA viruses and have positive sense and non-segmented genomes in the size ranging from 26 to 32 kbp and their genome are rich in guanine (G) and cytosine (C), which contains 32% to 43% (26-28). There are at least six open reading frames (ORFs) in RNA of CoVs. ORF1a/b, the first ORF, encodes replicas proteins and contains approximately two-thirds of the genome, while the other ORFs primarily encode four structural proteins including nucleocapsid (N), envelope (E), membrane (M), and spike (S) (29). The

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canonical set of genes encodes with the coding region, contains 5′ end-ORF1a/b replicase, spike, envelope, membrane, nucleocapsid-3′ end. There is a communal a 3′ terminal sequence and 5′ leader sequence, as well as subgenomic mRNAs (30, 31), with 5′ methylated caps and 3′ polyadenylated tails (32, 33). Also, the viral genome codes a number of nonstructural proteins (nsps) that include papain-like protease (PLpro), coronavirus main protease (3CLpro), and RNA-dependent RNA polymerase (RdRp) (30, 31).

Phylogenetic analysis of full-length genome sequences showed that SARS-CoV-2 had the most elevated similitude to SARS-CoV and it was less comparable to MERS-CoV (Figure 1). Given the near relationship between SARS-2 and SARS, examining the amino corrosive translocation totally different proteins may justify the basic and utilitarian contrasts between SARS-2 and SARS (3).

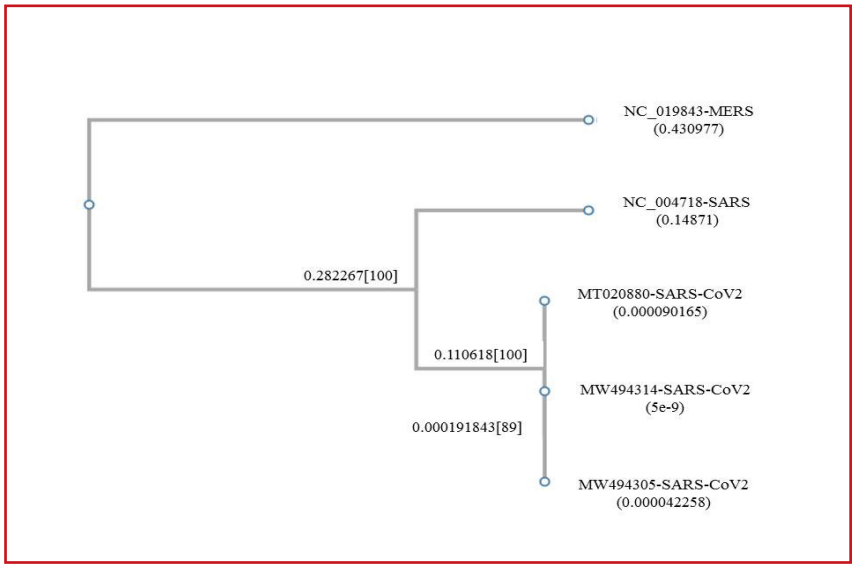

Figure 1. Phylogenetic analysis of complete genome of three human CoVs. MERS (NC_019843.3), SARS (NC_004718.3), and SARS-cov-2 (MT020880, MW494314, MW494305)

Genomic compression of SARS-CoV-2, MERS-CoV, and SARS-CoV

Figure 2 depicts the genome organization of SARS-CoV-2, SARS-CoV, and MERS-CoV, with the major differences between SARS-CoV-2 and SARS-CoV being in open reading frame-3b (orf3b), spike, and open reading frame-8 (orf8), especially spike S1 and orf8. Orf8 is a protein that serves as an accessory (29, 34, 35).

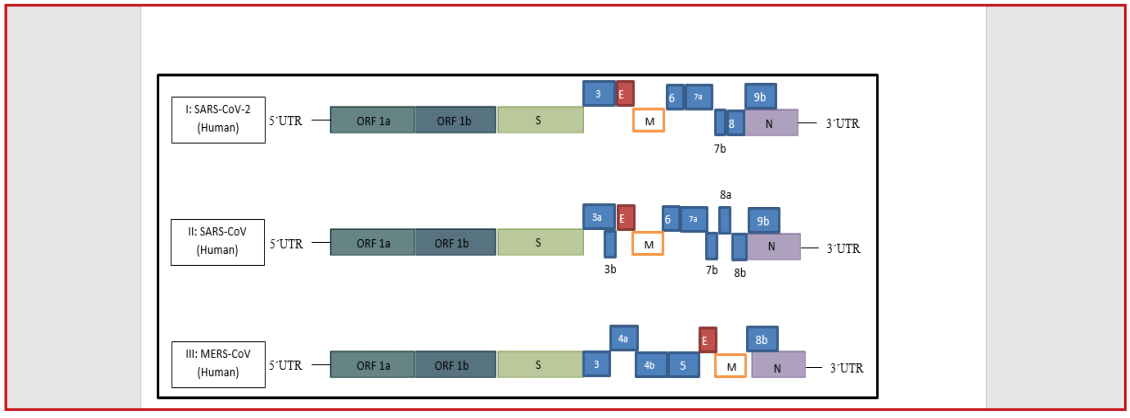

Figure 2. It is comprised of human (SARS-CoV-2, SARS-CoV and MERS-CoV) genome (35). In the SARS-CoV-2 genome, orf 1a/b encodes non-structural proteins (nsp), structural proteins such as spike (S), envelop (E), membrane (M), and nucleocapsid (N) proteins, and accessory proteins: orf 3, 6, 7a, 7b, 8 and 9b

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Studies on SARS- CoV-2 genome have demonstrated a very likeness to SARS CoV. The SARS-CoV-2 genome has 14 ORFs encoding 27 proteins that contain the eight accessory proteins (3a, 3b, p6, 7a, 7b, 8b, 9b, and orf14) and four major structural proteins (S, E, M and N) (36). A comparison between the SARS-CoV-2 and the SARS-CoV showed that there were some remarkable differences in the 8a, 8b, and 3b protein (36). Two accessory proteins (8 and 10) have been produced by SARS-CoV2 with no SARS-CoV homology. The preserved sequences ORF8 SARS-CoV differ from those of ORF8 SARS-CoV2 amino acid sequence. As these two SARS-CoV2 proteins are incompatible with the other CoV-strains, they can be used as a therapeutic objective (37). There is protein 8a, 8b in SARS however not in SARS-2. Length of 8b and 3b proteins in SARS is 84 and 154 amino acids, but ORF 8 and 3b in SARS-2 has 121 and 22 amino acids, individually (2). The NLRP3 inflammation and death of the pyroptotic cell can be activated by SARS-CoV orf8b, while no functional domain or motif identified is included in the new SARS-CoV-2 orf8 (35, 36). The first three differences are in the partial coding sequences of ORF1a/b (448nt, 55nt, and 278nt, respectively). The next two regions are in the S-gene (315 nt in SARS-CoV-2 and 80 nt, in SARS-CoV) partial coding sequences and the final region of variation is found in the coding sequences of the orf7b and orf8 genes (214nt) (38).

When the SARS-CoV-2 was compared with the MERS-CoV, it was discovered that the SARS-CoV-2 was more distant and less related to the MERS-CoVs (36). A comparison of the length of the amino acid sequence of polyprotein ORF1ab, S, E, M, and N between these three humans CoV is shown in table 1.

Table 1. Comparison of the length of the amino acid sequence of polyprotein ORF1ab, S, E, M, and N between SARS-CoV-2, SARS-CoV, and MERS-CoV

	Accession number	length
ORF 1ab hCoV		
SARS-CoV-2	QQV28594.1	7096 aa
SARS-CoV	NP_828849.7	7073 aa
MERS-CoV	YP_009047202.1	7078 aa
S protein hCoV		
SARS-CoV-2	QQV28596.1	1273 aa
SARS-CoV	YP_009825051.1	1255 aa
MERS-CoV	YP_009047204.1	1353 aa
E protein hCoV		
SARS-CoV-2	QQV28598	75 aa
SARS-CoV	YP_009825054.1	76 aa
MERS-CoV	YP_009047209.1	82 aa
M protein hCoV		
SARS-CoV-2	QQV28599.1	222 aa
SARS-CoV	YP_009825055.1	221 aa
MERS-CoV	YP_009047210.1	219 aa

	Accession number	length
N protein hCoV		
SARS-CoV-2	QQV28604.1	419 aa
SARS-CoV	YP_009825061.1	422 aa
MERS-CoV	YP_009047211.1	413 aa

The comparison of the genomes of SARS-CoV-2, SARS-CoV and MERS-CoV- is as follows:

SARS-CoV-2: SARS-CoV-2 has an RNA genome of 30,000 bases. The final genome of sequenced SARS-CoV-2 strain isolated in Nepal contains 8,903 (29.86%) adenosines, 5,482 (18.39%) cytosine, 5,852 (19.63%) guanine, and 9,574 (32.12%) thymine (39). The virus has a unique combination of polybasic cleavage sites in other β-coronaviruses, a unique feature that can result in other viruses being pathogenic and transmitted (40).The SARs-CoV-2 genome analysis demonstrated that the genome includes six main ORFs and that the identity of the nucleotide sequence is less than 80% with SARS-CoV. In the amino acid sequence of ORF1ab, however, seven conserved replicase domains are 94.4% similar to SARS-CoV ones. Genome analysis of SARS-CoV-2 genome indicates that it is similar to that with a sequence identity of 96.2%, the bat coronavirus (Bat coronavirus RaTG13). Furthermore, 93.1% of the receptor-binding spike protein is similar to Bat CoV RaTG13 (13, 41). Significant differences in the S gene sequence of SARS-CoV-2 were observed at the same time in comparison with SARS-CoV-2 containing three short N-terminal domain insertions and four of the five major residues of the receptor. One of the changes was the binding pattern and the unexpected furin spike at the S1 and S2 border of SARS-CoV-2 glycoprotein. This novel characteristic distinguishes SARS-CoV-2 from SARS-CoV and several SARS-related coronaviruses (SARSr-CoVs) (13, 39) (Figure 3-a).

SARS-CoV: this virus has a giant positive-strand RNA and its genome contains 29,727 nucleotides (~30 kb), with guanine or cytosine accounting for 41% of the genome. The broad genes ORF1a and ORF1b are two-thirds of the genome, which are the original order of the 5'-replicase (rep) genes. They found in the genomic body of this virus and they code two large polyproteins, pp1a with 486 kDa and pp1ab with 790 kDa. Moreover, the four ORFs downstream of rep genes are encoded into 3' pin S, E, M and N structural proteins. Genomic RNA is the gene rep products while the other viral proteins are the gene mRNAs. The SARS-CoV genome encodes, in addition to the original genes, eight other putative assistive proteins identified as ORFs 3a, 3b, 6, 7a, 7b, 8a, 8b, and 9b. The length of these proteins is 39 to 274 amino acids (13).

Though with some sequence homology of the SARS-CoV gene and structural protein, the accessory protein lacks substantial amino acid homology with other CoV virus proteins (13, 42) (Figure 3-b).

MERS-CoV: MERS-CoV genome has a length of 30,119 nucleotides and 10 proteins. ORF1ab and ORF1a (Two replicase polyproteins), S, E, M, and N (four structural proteins), and ORF 3, 4a, 4b and 5 (four non-structural proteins) are among the 10 proteins (13, 43). Also, the genes of accessory protein are divided into structural protein genes. In infected animals, these proteins can impair the innate immune response of the host (13, 44) (Figure 3-c).

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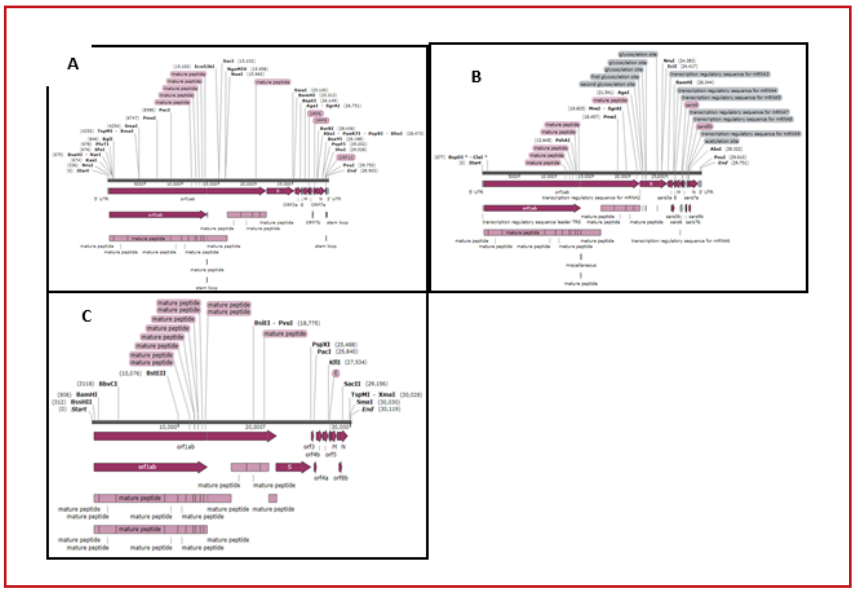

Figure 3. The structure of coronaviruses Genome. A) SARS-CoV-2 (COVID-19) Genome: 29,903 bp, B) SARS-CoV Complete Genome: 29,751 bp, C) MERS-CoV Complete Genome: 30,119 bp

Most of the proteins in SARS-CoV and SARS-CoV2 are strongly homologous (95–100%), according to proteomic similarity analyses (Table 2) (37, 45-48).

Table 2. Percent similarity of some proteins of SARS-CoV2 strain with SARS–CoV

proteins	Percent similarity	References
RdRp and 3CLpro protease	Over 95%	(37, 46-48)
S proteins	76%	(37, 46-48)
PLpro	83%	(47)

Full genome sequence profiling of SARS-CoV-2 from patients

The SARS-CoV-2 etiologist caused the COVID-19 outbreak to be widely distributed all over the world. In order to track the changes in this virus, detecting and studying the full SARS-CoV-2 genome sequence worldwide is important. The analysis of bioinformatics in 20 Iranian patients was shown 44 various nucleotide mutations that produced 26 nonsynonymous protein sequence mutations in relation to the complete reference SARS-CoV-2 genome sequence (NC 045512.2). Common mutations in these sequences are shown in table 3. In comparison with all present SARS-CoV-2 sequences, only some of the detected mutations were reported in Iranian data (table 3) (49, 50).

Table 3. Common mutations in SARS-CoV-2 sequence from Iranian patients (49, 50)

mutations	polyprotein	References
R207C	ORF1ab	(49)
V378I		
M2796I		
L3606F		
A6407V		
T8782C	ORF1a	(50)

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mutations	polyprotein	References
C15607T T18488C	ORF1b	(50)
T9561C	ORF1	(50)
C28144T	ORF8b	(50)
T28144C	ORF8	(50)
G26144T	ORF3	(50)
C21707T	S	(50)
T29095C C28854T G28878A	N	(50)
G29742A	3′-UTR	(50)

Two complete genome sequences of the SARS-CoV-2 obtained from clinical samples of patients with COVID-19 in Hubei China (named WH19004-S and GX0002), and ORF7a and ORF8 of WH19004-S were sequenced by the Sanger sequencing method and two SNPs were recognized: T/C, nt 27,493 in ORF7a and T/C, nt 28,253 in ORF8 (51). 8,582,968 single-nucleotide Polymorphisms was reported from 1980 Italian and Spanish Covid-19 patients (35). Also, another complete SARS-CoV-2 genome sequence from a Nepalese patient was reported that the contamination was obtained in China (Wuhan), and transferred to Nepal. The genome was sequenced by The Illumina MiSeq system and the BWA-MEM 0.7.5a-r405 algorithm was applied. After trimming, a total of 9,891,431 sequences involved in the reference-based arrangement, with 9,887,093 (99.96%) of them mapped to the reference genome of SARS-CoV-2. In the United States, there is a clear gender difference in the ORF8 protein mutation 27964C>T-(S24L). The large proportion of female ORF8 S24L mutation patients are indicative of the most likely event of S24L among the female population in the United States. Therefore, a female-dominance pattern is present in the mutation 27964C>T-(S24L). C>T mutations are actually preference for women as well (52).

Researchers around the world are still researching the genetic sequence profiling of COVID-19 patients due to the considerable amount of epidemiological, experimental, clinical, biophysical and multiple studies involved in the analysis of genome sequencing and single-nucleotide polymorphism (SNP) (figure 4).

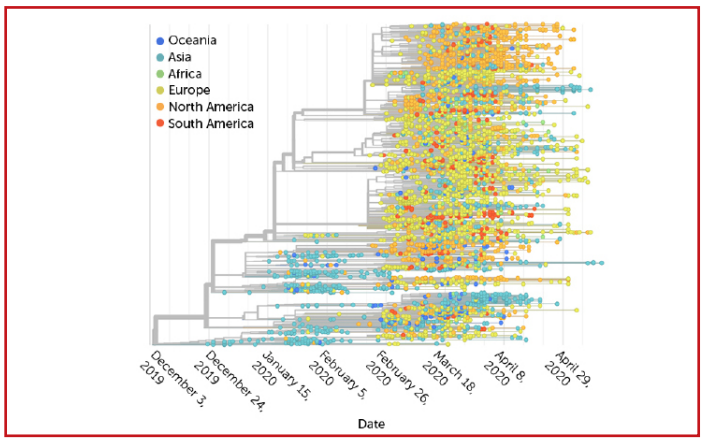

Figure 4. Map of the expansion of SARS-CoV-2's genetic changes, December 2019–May 2020 (https://www.sciencenews.org/article/coronavirus-covid19-mutations-strains-variants)

Discussion

Despite advances in the medical field, the emergence or re-emergence of novel pandemic viruses remains a persistent problem around the world (53). Risky factors implicated in the emergence or re-emergence of viral infectious diseases or disease spreads including human, environmental, and virus-related factors. As a result, drawing these contributory risk factors is critical for disease surveillance, prevention, and control in viral infectious illnesses (53). The growth of the pandemic COVID-19 has attracted interest in coronavirus biology and pathogenesis. An in-depth understanding of the interaction between coronaviruses and host factors may help provide better support for disease patients and help treat lung infections caused by viruses (50). Many people are asymptomatic. The mortality rate is estimated at 2 to 3% (54). However, hypertension, diabetes and other obesity-related and cardiovascular diseases have also been informed about the majority of deaths in elderly patients and men. The comparative role of clinical risk factors for determining Covid-19 seriousness has not been yet explained (35). The age and coexistent health conditions including cancer and cardiovascular diseases have dramatically increased morbidity and mortality by COVID19. Human genetic factors can lead to the wide transmission capabilities of SARS-CoV-2 and to the continuous severe disease found in a small but significant number of people infected, but those factors are not entirely evident (55).

This new outbreak of the virus has called the economic, medical and health infrastructure of the world into question. In the present study, we examined and composed the SARS-CoV-2 genomic structure with the SARS-CoV-2 and with the use of phylogenetic analysis and reviewing papers, in order to take into account the importance of knowing the genomic MERS-CoV, SARS-CoV, and SARS-CoV-2 information, it may provide insight into how SARS-CoV-2 escapes immune response to host because of a very limited number of SARS-CoV-2 data (8). Additional genomic regions are found in 80% of SARS-CoV and 50% of MERS-CoV RNA sequences with SARS-CoV-2 RNA (48). It has 20-30 more amino acids in its spike protein than SARS-CoV and other nearby coronaviruses. Consequently, SARS-CoV-2 has similar immune escape strategies but no further mechanism has yet been found (5, 56, 57). It is highly probable that MERS-CoV and SARS-CoV have been transmitted from bats to palm civets, and that MERS-CoV was transferred to humans from bats to dromedary camels (18, 22). Genomic information of hCoVs promotes an understanding of the pathogenesis and origins of hCoVs. Therefore, stronger knowledge about viral genomic is essential to prevent hCoV outbreaks by developing accurate strategies such as the development of diagnostic systems, potential medicaments, and vaccine candidates (58).

Conclusion

Genetic comparisons between the genomes of various viruses in a family can provide useful information for designing targeted therapies for novel emerging members. As a result of genetic selection, viruses are constantly changing. Changes in the virus genome can lead to changes in viral protein function. These changes can lead to new viral serotypes or change in their virulence. Therefore, the knowledge of the genomic structure of the virus can help in designing efficient antiviral drugs - as well as vaccine development. Direct sequence of RNA has also the potential to substantially advance genome studies of complex populations of viruses by showing long-term interactions with individual full-length viral RNA haplotypes.

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Conflict of interest

The authors declare that there is no conflict of interests.

Abbreviations

BWAMEM: Burrows-Wheeler Aligner MEM algorithm

CoVs: Coronaviruses

hCoVs: Human coronaviruses

SARS: Severe Acute Respiratory Syndrome

MERS: Middle East Respiratory Syndrome

COVID-19: Coronavirus Disease 2019

RdRp: RNA-dependent RNA polymerase

PLpro: papain-like protease

3CLpro: 3C-like protease

nsps: nonstructural proteins

ORF: Open Reading Frame

SNP: Single-Nucleotide Polymorphism

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