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# SARS-CoV-2 continued Evolution and Pathogenic Differencein Human Hosts

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ABSTRACT

*The epidemic covid 19 originated from Wuhan, China during December 2019 in and since then spread innot only in China but also throughout the world and raised a major international concern. With the continuous extensive transmission studies are evidencing for an amount of molecular differences among SARS-CoV-2 found at the originating site and other related regions globally covid 19,Genome sequencing has evidenced the presence of dissimilar strains in different regions. Severity of disease varies in countries where few regions are affected more than others virus. This evolving nature of the virus not only can affect its diagnostic methods but also manufacturing drugs or vaccine.*

## 1. Introduction

December 2019 in Wuhan, China strange variety of pneumonia from a new type of corona virus revealed in a group of patients and was initially named as 2019 novel coronavirus (2019-nCoV) by World Health Organization (WHO) on 7thJanuary. WHO reported on 13 July 2020of approximately 80% of COVID-19, cases were reported from 10 countries whereas 50% belong to just two countries (Situation Report,2020). At present, SARS-CoV-2 holds mortality rate of approximately 3.4% [Lai et al.,2020. WHO offered a range of early seroepidemiological investigation protocols instantaneously after the emergence of new virus. The incidence rate of disease got doubled in each 7.4days in early stage and the basic reproductive number was expected as 2.2 (li et al.,2020).

Transmission can occur not only from Respiratory droplets (respiratory activities such as talking, coughing and sneezing) and direct contact, but also fecal-oral transmission, fomite transmission (transfer via an object), perinatal (intrauterine) transmission(Zhou et al.,2020). Corona virus stays alive on metallic, glass, plastic surfaces for up to 9 days. Only few microbiocidals are found helpful efficiently inactivated When staying on dead surfaces by the help of 0.1% sodium hypochlorite/ 62–71% ethanol/ 0.5% hydrogen peroxide within1minutes(Sattar et al.,20202).

## 2. Pathogenicity and transmission

The patients may have asymptomatic as well as symptomatic features, although asymptomatic persons can also transmit virus(Bai et al.,2020). Common symptoms include fever, cough and myalgia, lymphopenia, leucopenia and radiographic evidence of pneumonia. Headache, dizziness, abdominal pain, diarrhea, nausea, and vomiting are some of the less common symptoms. Old aged patients possible to have comorbidities including diabetes, hypertension, cardiovascular diseases and cerebrovascular disorders are more susceptible for intensive care. During Hospitalization may face problem as acute respiratory syndrome (ARDS), arrhythremia, aggravate

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urea and creatinine blood levels (Wang et al.,2020) (Xu et al.,2020). Exact source of COVID-19 virus is still ambiguous Since, similarity was found between the SARS CoV- 2 and Bat-CoV RaTG13 (a gene detected from a bat) suggested bat as an initial host and more studies recommended pig or pangolin or any zoonotic agent as a probable intermediate host (Sun et al.,2020). Diagnosis of CoVID-19 mainly includes its nucleic acid isolation then RT-PCR (Real Time Polymerase Chain Reaction) and testing of Lower respiratory tract samples, swabs, nasal swabs, nasopharynx or trachea extracts, sputum or lung tissue, blood, feces etc provide an advanced rate of positive detection. Chest Computed Tomography Scan (CT scan) is also a main technique for diagnosis (Yu et al., 2020, Wang et al., 2020). Acute Respiratory Distress Syndrome (ARDS) is the main cause of fatality in COVID-19 (Bonow et al.,2020). Severely infected persons evidenced for Cytokine Storm Syndrome (CSS) and Acute Respiratory Distress Syndrome (ARDS), Sepsis and multi-organ failures. A cytokine storm seen in Secondary haemophagocytic lymphohistiocytosis (sHLH) is seen in severe COVID-19 disease, which shows increased interleukin (IL)-2, IL-7, interferon-γ inducible protein 10, granulocyte-colony stimulating factor, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α (Huang et al.,2020).

## 3. Covid 19 Virus Divergence

Studies suggest a distinctive feature in Covid 19 virus genome sequence, receptor-binding domain (RBD) present in spike protein seems similar with human Angiotensin convertingenzyme-2 (ACE2) receptors and in additionshow polybasic cleavage on thelink of both subunits S1 and S2 of spike, in fact determinethe infectiousness of the virus (Lu et al., 2020). SARS-CoV-2 with its two major types, S and L in which Ltypeprevalent more, in approximately 70% of the cases (Tang et al.,2020).COVID-19 virus contains four structural proteins: Spike (S), Envelope (E), Membrane (M) and Nucleocapsid (N). These proteins encodes for viral polymerase (RdRp), RNA synthesis materials and ORF1a-ORF1b (two types of huge nonstructural proteins (Chan et al.,2020). S is a surface protein of the virus and provides a shape of crown and makes an interaction between the host cells and helps in endocytosis of the viral particle into the host cell by binding to the angiotensin-converting enzyme 2 (ACE2) receptor. E protein a viral transmembrane protein supports the assembly of the visions by forming ion channels inside host cell (Gupta et al.,2020). E and M types act as small transmembrane proteins. Nucleocapsid (N) acts on to makecopy and formation of recombinant proteins. CoVs extremely recombine which is the outcome of repetitively developing transcription errors and RNA Dependent RNA Polymerase (RdRP) jumps (Woo et al.,2020)

Total seven number of corona viruses is found accountable for respiratory complications in humans so far (HCoVs). The diagnoses of virus, its Pathogenic mechanism then vaccine and drug developments the entire process based on to know about the whole genome of COVID-19. SARS-CoV-2 virus genome samples collected globally confirm the genetic diversity and evolution because of Mutations (Phan et al., 2020). It is evidenced genome sequences of COVID-19 viruses in humans have gone through mutations over these past months. NCBI database assembled more than 400 genomes of SARS-CoV2.

While the previous Severe acute respiratory syndrome (SARS-2002) was not considered as more contagious for human beings(Chang et al.,2020). It is urgently desirable to found a helpful safe and efficient antiviral against COVID-19. Chloroquine sulfate and Hydroxychloroquine sulfate are the drugs which permitted by FDA (Zhang et al.,2020). Drug Chloroquine is used against malaria found inexpensive and safe for old aged persons (Gao et al.,2020)

Chloroquine (CQ) and Hydroxychloroquine s (HCQ) with a combination of Hydroxychloroquine and Azithromycin have been used as first-line treatment drugs in most of countries (Gautret et al.,2020) may cause side effects including possibility of cardiac arrhythmias, gastrointestinal responses and retinal damage especially when used for long time (Koumaki et al.,2020)..Remdesivir, Lopinavir (LPV) and Ribavirin (a guanosine analogue) also inhibits viral replication (Zhai et al.,2020). Some drugs such as anti-influenza drugs previously used for the treatment of SARS and MERS, Umifenovir, Oseltamivir, are still under investigation (Wang et al.,2020). Randomized control trials are continued to discover an efficient drugs and vaccines (Gao et al.,2020). Numerous of pharmaceutical companies around the world attempted to isolate antibodies to develop COVID-19 test kits, vaccines and antibody for its treatment.

COVID-19 virus show similarity with Ebola virus and others four flu corona viruses (HCov-OC43, HCov-229E, HCov-NL63 and HCov-HKU1) and more common with SARS. COVID-19 or Corona Virus Disease 2019 strain belongs to Betacoronavirus group 2B and found 70% genetically similar to that of SARS-CoV (Hui et al., 2020), with a genome of length 29,903 base pairs and ordered in to 11 genes coding for different proteins as Spike protein (Lu et al.,2020), encoding 12 open reading frames (ORFs) (Kim et al.,2020). Genome sequencing concluded about the 86.9% genome similarity of 2019-nCoV to SARS-CoV genome (Chang et al.,2020). Corona viruses were identified as pleomorphic, enveloped virus containing crown shaped peplomers of 80-160 nM size and 27-32 kb with positive polarity. International Committee on Taxonomy of Viruses (ICTV) classified the virus in 4 genera then 28 exclusive species. 4 genera of contagion include α-CoVs,

β-CoVs, ᵞ-CoVs and ᵟ- CoVs. Alpha and Beta strains are found to infect Mammals while Gamma and Delta transmit disease to both birds and humans (Sahin et al., 2020).

Chinese researchers of Peking University in Beijingdescribed in National Science Review two distinct lineages of SARS-CoV-2, which they termed "S" and "L." The two clusters of genomes were labelled as S (Serine) and L (Leucine) types and after analysis of 103 viral sequence samples around 70% were of the L lineage,researchers termed it an "aggressive type."

Covid 19genome also codes for two overlapping polyproteins including polyprotein 1a (PP1a) and polyprotein 1ab (PP1ab); PP1a being a truncated version of PP1ab code for 16 non structural proteins (NSPs) including proteases (3C-like protease and Papain-like protease) and RNA-processing enzymes like RNAdependent RNA polymerase, Helicase, 3'-5' Exonuclease, Endoribonuclease, Guanine N7-methyltransferase, 2'O-ribose methyltransferase and ADP ribose phosphatase (Wu et al.,2020).

In addition to structural and NSPs, SARS-CoV-2 genome also codes for two other viroporin named as ORF3a and ORF8 (Castaño-Rodriguez et al., 2020). SARSCoV2 genomic feature was identified bySequence analysis of the samples collected from various countries including India, Italy, USA, Nepal and Wuhan. After analyzing and comparing to SARS-CoV Wuhanvirus found close withSARS-CoV. At least one type of variation like deletions, misaligned and frameshift mutations were established in all other SARS-CoV2 proteins except ORF6, ORF10 and ORF14 andthe maximum number of mutations were recognized in Indian genomesited in ORF1ab, nsp2, ORF8,nsp3, protein helicase, and spike surfaceglycoprotein(Sardar et al.,2020). The changes seen in the SARS-CoV-2 genome are increasing its virulence(Pattabiraman 2020).

Studies suggest SARS-CoV-2 genome can be classified into at least 10 distinct groups. In SARS-CoV-2 phylogeny, most of the original isolates of China belongs to B clade and Isolates across the world to the A clade. The data (5,234 complete genomes) by 386 groups across the world explains that A2a is the most commonly sequenced clade (next strain, 2020). The genome sequencing of Nepalese patients established that genome of BetaCoV/Nepal/61/2020 from coordinates 1to 29811 was found similar to sequence of Wuhan-Hu-1 from 16 to 29826 (29810/29811), only except a site 24019. It is a silent mutationat the spike gene (Codon AAC to AAT). Five mutations were recognized including T8782C (in ORF1a, codons AGT to AGC, silentmutation), T9561C (in ORF1a, codons TTA to TCA, non-silent mutation), C15607T (inORF1b, codons CTA to TTA, silent mutation), C28144T (in ORF8b, codons TCA to TTA, nonsilent mutation), and T29095C (in nucleocapsid, codons TTT to TTC, silent mutation)(Bastola et al.,2020). In another study SARS-CoV-2 in patients of Indian origin exposed the possibility of multiple point mutations of 36 nucleotide deletion in ORF8 (Gaurav et al.,2020).

Genome sequence analysis of complete genomic sequence of virus confirmed that about 13 strains in countries such as China (7/85),Thailand (2/2),Japan (2/9),USA (1/32),and South Korea (1/9) mayprobably be linked to the first generation COVID-19 virus (Pattabiraman et al.,2020). Professor Li Lanjuan and her colleague researchers analyzed viral strains isolated from 11 randomly chosen Covid-19 patients from Hangzhou in the Eastern province of Zhejiang, show the deadliest mutations in these patients also found in most of the patients across Europe, while the milder strains were the predominant varieties found in Washington state and some other areas of the US. Around 100 sequenced genomes analysis to see changes in mutation frequency. A Single nucleotide with only one mutation can result into conformational change in the viral structural protein.A point mutation of C241T, in an un-translated region at 5' endproduced significant effects on the replication of the virus in patients. Another mutation was seen in the protein ORF1ab, namely, C1059T, which changed the uncharged polar Threonine into the hydrophobic Isoleucine(Draghi &Ogbunu,2020). The single deletion occurred at different locations in these strains. Threonine interacts through hydrogen bonds with the polar amino acids deep within the proteinsthus create a bend in proteins structure because of the relative positions of Glycine and Proline. Isoleucine though, disrupts such kind of bend because it cannot form hydrogen bonds, and promote hydrophobic interactions with phenylalanine residues around it (Biorxiv,June 2020). The G28221T substitutes a stop codon for glutamic acid, so that the C-terminal of ORF8 is truncated by the deletion of a 36-nucleotide long segment. In essence, this corresponds to the cleaving off of the fourth beta-strand in this region, probably disrupting the function of the protein. Finally, the G28371T mutation substitutes serine into the hydrophobic residue isoleucine, in a region of the N protein distant from any functional domain and, therefore, unlikely to produce much effect on the structure of the protein. However, this is surrounded by a site for glycosylation, which is an essential post-translational modification of the protein that confers virulence. This mutation could, therefore, have a marked impact on viral protein glycosylation(Biorxiv 2020).

Hyeryun Choe, Scripps Research virologist founda new mutation 'D614G' in spike protein of SARS-CoV-2 straindominant and much more infectious across the worldcompared to withoutmutation due to 4 or 5 times density of functional spikes after mutation. According to them D614G mutation in the SARS-CoV-2 spike protein decreases S1 shedding thus increases infectivity. During February, no sequences in GenBank database illustrated D614G mutation. But it appeared by March in 1 out

of 4 samples andincreased up to 70 percent during Maywhen more samples studied (Zhang et al,2020). Another study done on genome from various countries explainstwo strains SARS-CoV-2a and SARS-CoV-2g which can be differentiated based on a unique 3 nucleotide.Three nucleotides show changes as a bloc in SARS-CoV-2 genome. This bloc mutation (GGG>AAC) affects the nucleocapsid (N) protein of the virus which is crucial for virus replication. So (GGG>AAC) mutation negatively affects the N protein and reduce its infectivity so it can make clear why in the lower number of COVID-19 cases areas where SARS-CoV-2a is predominant such as Portugal, Netherlands, Belgium while countries/areas (USA, Spain, France, and Germany) SARS-CoV-2g predominates seem highly contagious(Ayub,2020).

## 4. Conclusion

The majority of mutations may not produce changes in virus but a few may result in to harmful. Thus before developing a vaccine or potential drugs it is important to measure mutations in the virus and could result in to waiting more for accurate cure for the illness (The Lancet, 2020).

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