Higher Omicron JN.1 and BA.2.86.1 Coronavirus Transmission Due to Unique ¹⁷MPLF Spike Insertion Compensating ²⁴LPP, ⁶⁹HV, ¹⁴⁵Y, ²¹¹N and ⁴⁸³V Deletions in the Spike

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Abstract

Mutation, deletion and insertion in the spike likely select RBD in a favorable 3-D structure to interact with ACE-2 receptor of human cells for coronavirus entry. Our goal is to characterize the newly spreading JN.1 subvariant and related omicron coronaviruses. BLASTP search found a ¹⁷MPLF four amino acid insertion in omicron BA.2.86 and BA.2.86.1 subvariants and its precedent JN.1 subvariant which had unique L452S (L455 in Wuhan) spike mutation. The JN.1 variant also contained 2375 SGF deletion in ORF1ab, ^{24}LPP , ^{69}HV , ^{145}Y , ^{211}N (^{208}N in BA.2) and ^{483}V (^{480}V in BA.2) deletions in the spike, ^{31}ERS deletion in N-protein and 26nt deletion in 3'-UTR (NC 045512.2). Many unique JN.1 spike mutations (242N=H249N, 261D=A268D, 352T=K360T, 400K=R407K, 442H=P449H, 449W=L456W, 474K=N485K, 480K=A488K and 566V=A574V) might be also important. The BLASTN search with insertion oligo found over 4984 JN.1 related sequences (10.1.2024) in the NCBI Database and were well distributed in America, Europe and Japan. Although, JN.1 acquired the 69HV deletion lately but did not generated from BA.4 or BA.5 lineages and it was solely generated from BA.2.86 variant. Swiss-Model detected a wing structure with basic amino acid in the middle of tripartite spike of JN.1 and important ACE-2 first interacting surface amino acids were changed. The small M protein of JN.1 had D3H, A63T and A104V mutations but Swiss Model showed no gross change in 3-D structure. Further, four JN.1 specific ORF1ab polyprotein mutations were detected: T170I mutation in nsp1 as well as D1600N, K1973R mutations in nsp3 protease and R3821K mutation in nsp6. Astonishingly, after a long journey of XBB.1.5.1 to XBB.1.5.100 subvariants spread, a sudden five amino acids deletion (¹⁷⁶EGKEG and¹⁸⁰EGKQG in Wuhan) in the spike of XBB.1.5.103 subvariant was found. The ORF8 immune-regulatory protein expression was abolished in all XBB.1 subvariants including XBB.1.5.103 and XBB.1.16.23 as expected due to termination codon mutations (AAA=TAA, CAA=TAA, GGA=TGA). But such ORF8 gene mutation (GGA=TGA) was also found in ongoing dominated JD.1.1, FL.1.5.1, HV.1 and EG.5.1.1 subvariants, derived from XBB.1 lineage. The FL.1.5.1 variant also has ⁸²GHV deletion instead ⁸²GHVMV in the nsp1 protein as well as a 27nt deletion (27887 5'-aac gaa cat gaa att tct tgt ttt ctt-3') in the ORF7a gene. Partial or no expression of nsp1, ORF7a and ORF8 regulatory proteins cause coronavirus more immune deficient and less pathogenic. The spread of JN.1 has sent an alarm among health officials worldwide. It is worthwhile to see if BA.2.86.1 and JN.1 coronavirus goes nsp1 or OR7a deletion and ORF8 termination codon mutation with time lowering pathogenicity.

Keywords: JN.1 Omicron Coronavirus, ¹⁷MPLF Spike Insertion, BA.2.86.1 Subvariant, XBB.1.5.103 Subvariant, ¹⁸⁰EGKQG Spike Deletion

1. Introduction

So far round 7000000 people have died between 2019-2024 due to deadly Delta, Alpha and to some extent Beta and Gamma lineages of SARS-CoV-2 [1, 2]. However, Mutation, Deletion and Insertion in omicron coronaviruses have reduced the viral tire and disease severity [3]. Still, NCBI Virus Database is depositing omicron COVID-19 sequences every day demonstrating that COVID-19 era has not been ended yet. Coronaviruses (family, Coronaviridae) are enveloped viruses with a largest positive sense, single-stranded RNA genome of 30kb. On genetic and antigenic criteria, CoVs have been organised into three groups: α -CoVs, β -CoVs, and γ -CoVs [4]. Coronaviruses (2003-2024)

primarily infect birds, mammals and human, causing a variety of lethal respiratory diseases resembling the common cold, to lower respiratory tract infections such as bronchitis, pneumonia, and even severe acute respiratory syndrome (SARS) [5, 6]. The Covid-19 (SARS-CoV-2) preferably infects human lung cells. The virus enters cells through ACE2 receptor-mediated endocytosis. The receptor ACE2, was abundant in lungs AT2 alveolar epithelial cell as well as cells in the kidney, nose, heart and blood vessels [7, 8].

SARS-CoV-2 had structural proteins (S, M, N, E) at the 3'- end and two polyproteins, ORF1ab, ORF1a (7096aa and 4405aa)

were coded in same reading frame from 5' of 2/3 of the genome which were degraded into sixteen (nsp1-nsp16) non-structural proteins [9]. The ORF1ab generates sixteen functional peptides proteolytically: Nsp1(1-180aa), Nsp2(181-818aa), Nsp3(819-2763aa), Nsp4(2764-3263aa), Nsp5(3264-3569aa), Nsp6(3570-3859aa), Nsp7(3860-3942aa), Nsp8(3943-4140aa), Nsp9(4141-4253aa), Nsp10(4265-4392aa), Nsp11(4393-4400aa), Nsp12(4401-5324aa), Nsp13(5325-5925aa), Nsp14(5926-6462aa), Nsp15(6453-6798aa) and Nsp16(6799-7096aa) [10]. The functions of the most sixteen enzymes were reported: Trans-activator (nsp1), RNA topoisomerase (nsp2), two proteases (nsp3 and nsp5), RNA-dependent RNA polymerase (nsp12), RNA helicase and capping methyltransferase (nsp13), nucleases (nsp14 and nsp15) and methyl transferases (nsp16) and accessory proteins (nsp7, nsp8, nsp9 and nsp10) [11-18]. The ORF1ab protein was reported as 7096-7092 AAs in different variants. The spike protein (1273 AAs) is a trimeric class 1 transmembrane glycoprotein and it's RBD domain (335-515 aa) acts as receptor binding domain to bind ACE-2 receptor of host lung cells for virus entry [19]. The spike protein 1-13 AA acts as signal peptide and the S1 subunit (14-685 AAs) containing RBD domain and S2 subunit (686 to 1273 AAs) are important due to furine cleavage. Spike protein also contains fusion contact peptide (788-806 AA) as well as two hepta-peptide (HPPHCPC) repeats at 1163 and 1213 positions [20]. The ORF3a, ORF6, ORF7a, ORF7b, ORF8, ORF9 and ORF10 are small regulatory proteins also coded from 3' end of the SARS-CoV-2 genome and have roles in regulating cellular genes [21-26].

Spike protein in COVID-19 greatly varied in different lineages. Spike protein is 1273aa in Wuhan but it has changed in Alpha lineage to 1270 AA due to deletions of 69HV and 145Y positions; in Delta variant spike is 1271aa due to ¹⁵⁶FR deletion only. Spike protein of omicron BA.1 variant is 1270aa due to 69HV, 143VYY and ²¹²L deletions as well as ²¹⁵EPE three amino acid insertion [27-30]. The Spike protein of omicron BA.4 and BA.5 corona viruses is 1268 AA due to deletions of ²⁴LPP and ⁶⁹HV. Spike protein of omicron BA.2 has 1270 AAs due to ²⁴LPP deletion but no ⁶⁹HV and ¹⁴³VYY deletions or ²¹⁵EPE insertion [3, 10]. The 69HV spike deletion found in B.1.1.7 first but also acquired in omicron BA.1, BA.4 and BA.5 variants but not in omicron BA.2 variant. Among the other structural proteins N-protein (419 AAs) binds to leader RNA of replicating corona virus and also regulates host-pathogen interactions. Three AAs deletion (³¹ERS) was found in N-protein (416 AAs) of all omicron corona viruses (BA.1/2/4/5) and was very useful for diagnostics. Three amino acid deletions (3675SGF) were found in ORF1ab protein (nsp6 protein region) of Alpha and Omicron BA.2 and BA.5 (ORF1ab=7093) but at the same region ³⁶⁷⁴LSG deletion as well as extra ²⁰⁸³S deletion were found in omicron BA.1 corona virus (ORF1ab=7092 AA). Interestingly, no ORF1ab deletions in notorious Delta variant (ORF1ab=7096 AAs). Whereas, a three amino acids 141KSF deletion in the nsp1 protein was found in omicron BA.4 variant only (ORF1ab=7090 AAs) and such change was utilized to detect BA.4 omicron variant [31, 32]. Further, D614G mutation was detected in all variants since March, 2021 ongoing and such mutation increased 80% higher transmission [33]. The N501Y spike mutation was appeared first in Alpha (B.1.1.7) variant but also located in omicron variants BA.1, BA.4, and BA.5 followed by recent BF.1, BQ.1, XBB.1, JN.1, HV.1 and FL.1 lineages and sub subvariants [34]. The N501Y mutation increased transmission by more than 20-50% as well as immune escape. The P4715L ORF1ab mutation at RdRP was found in all variants since March, 2020 similar to D614G mutation. As N501Y and D614G both mutations appeared in omicron BA.1, BA.4 and BA.5, such viruses gained more spread than alpha, delta as well as BA.2 corona viruses but gave mild pathogenicity due to 25 more mutations in the spike and 26nt 3'-LTR deletion [20, 26]. The BA.2.12.1 lineage gained L452Q mutation facilitating immune-escape and high infectivity. However, BA.2.75.2 sub-lineage carrying additional R346T, F486S and D1199N mutations in the spike protein and gained more mutations and rearrangement to produce XBB variant. The BA.4.6 variant with R346T and N658S mutations was one of the dominating variants [26]. Delta variant contained L452R immune-escape mutation which also gained by omicron BA.1 as well as BA.4 and BA.5 variants. The BA.4 and BA.5 variants also gained important F486V mutation to produce immune escape similar to L452R mutation. A single mutation (E484K) present in SARS-CoV-2 Beta (B.1.351) and Gamma (P.1) lineages may alter the neutralising activity of convalescent (infected with previous COVID-19 strains) and post-vaccination polyclonal serum. Delta (B.1.617.2) variant has no N501Y mutation and spread of such viruses were diminished since 2021 due to vaccination. The P681R mutation in Delta variant was replaced by P681H in all omicron variants (BA.1/2/4/5). The Gamma (P.1 or B.1.1.28.1) variant had 3675LSG deletion in the ORF1ab protein (nsp6 region) and such information was used to make DelORF1ab3675-P1 oligonucleotide specific for P.1 variant [35].

Data analysis detected one amino acid deletion (140Y=TAT; 145Y in B.0) in spike in BA.4.6, BO.1.5, BO.1.8, BO.1.14, BO.1.1.5, XBB.1 as well as related BU.1, BW.1, CP.1 and CQ.1 subvariants. But Y140 deletion was not detected in BA.2.75, BF.7, XBD, BQ.1, BQ.1.1, BQ.1.2, BQ.1.10, BQ.1.12, BQ.1.16, BQ.1.19, BQ.1.22, BQ.1.1.1, BQ.1.1.4, BQ.1.1.12 and related BK.1, BN.1, BM.1.1.1, BU.1, CA.1, CH.1.1 subvariants [36]. Spike protein mutations were rampant in omicron coronaviruses. The 91% nucleotides changes in spike protein of BQ.1 variant was resulted in AA changes whereas only 52% nucleotides changes resulted in AAs changes in ORF1ab polyprotein [37]. The spike N460K and K444T mutations in BQ.1 may be important driving force for immune-escape similar to F486S and N480K mutations in BA.2.75 subvariant and related XBB.1 subvariant. Further, the R346T mutation as found in BA.4.6 and BF.7 was regained in the spike of BQ.1.1 and BA.2.75.2 or related recent lineages CH.1, BM.1 and CA.1 to enhance immune escape and infectivity (>80%). The L452R and F486V spike mutations were main drivers of Omicron BA.2 conversion to BA.4 and BA.5 in presence of ⁶⁹HV deletion and 30nt deletion in 3'-UTR. Whereas ²⁴LPP spike deletion and ³⁶⁷⁵SGF ORF1ab protein deletion were found in all Omicron viruses including BQ.1, XBB.1, HV.1 and JN.1.

In USA, Wuhan D614G first peak occurred between March-

August, 2020, Alpha (B.1.1.7) 2nd peak between January-June, 2021 followed by 3rd peak of Delta (B.1.617.2, AY.X) between June to December, 2021 [27]. Since last week of December, 2022 4th peak of Omicron BA.1 variant (B.1.1.519) spread was evident followed by BA.2 variant spread in April, 2022. From June-July, 2022, omicron BA.4 and BA.5 variants are increasing worldwide [28]. From November 2022 we found the spread of BQ.1 subvariants and from March 2023, we find spread of XBB.1 lineage. In August 2023, we detected more than 448 249RWMD spike insertion sequences spread in the USA and Europe. But such lineage was not prominent at the end of 2023 [37]. Where as in December 2023 new sub-subvariants like XBB.1.16, XBB.1.5, EG.5.1, HV.1, FL.1.5, JN.1 and JD.1.1 were the major omicron coronaviruses sequences were deposited in the NCBI virus database [29, 30]. Similarly, we detected ORF7a protein deletions in BQ.1 variant and ORF8 termination codon mutations in XBB.1 lineage as well as 141KSF, 82GHV and ⁸²GHVMV deletions in the nsp1 protein of omicron BA.4 variant [22, 24, 26]. All these changes caused recent corona viruses weak and non-life threatening with very low viral titer as compared to Alpha and Delta variants [36, 37]. In this communication, we detected a continuous deletion and insertion in the spike of new corona virus variants like BA.2.86.1, JN.1, XBB.1.5.103 and HV.1 [38, 39]. We discussed the potential issues of such changes for its pathogenicity and worldwide transmission as also reported in many newspapers recently.

2. Materials and Methods

The BLAST search was done using web portal www.ncbi.nlm. nih.gov/blast and retrive of covid-19 and other corona viruses cDNA sequences were done using web portal www.ncbi.nlm.nih. gov/nucleotide or protein. NCBI Primer Design Software was used for primer selection and Oligoanalyzer 3.2 software was used to analyse primer dimmer and hairpin structure. MultAlin Software and CLUSTAL Omega Software were used to multiple align of protein sequences and NCBI BLAST seq-2 analysis portal (www.ncbi.nlm.nih.gov/blast) used to analyse homology between two sequences. NCBI PubMed portal (www.ncbi.nlm. nih.gov/pubmed) used to retrieve references and papers. NEB DNA cutter software was used to restriction map the DNA fragment. Swiss-Model software was used for 3-D structure prediction (http://swissmodel.expasy.org/interactive/Jpr JmW).

3. Result

Multi-alignment of spike proteins from highly spreading randomly selected six subvariants demonstrated a ¹⁷MPLF four amino acids insertion at 16 position of spike in omicron JN.1 variant ahead of ²⁴LPP deletion. But such insertion was not detected in highly spreading HV.1, EG.5.1.1, JD.1.1, XBB.1.16 and XBB.1.5 new subvariants that were highly appeared in the NCBI Virus Database during December, 2023 (NIH, USA). Similarly, a ¹⁸⁰EGKQG deletion (¹⁷⁶EGKEG in Omicron; ¹⁷⁶VGKEG in XBB.1.6.23) in the 176 position of spike of XBB.1.5.103 subvariant (see, multi-alignment data, figure-1, lower portion) was also found. The genomes of such variants were multi-aligned and the data was presented in figure-2. We detected the ¹⁷MPLF insertion (ATGCCGCTGTTT) in JN.1 and 176EGKEG deletion (GAA GGA AAA GAG GGT) in XBB.1.5.103 in the genome wide search. Further, ²⁴LPP, ⁶⁹HV, ¹⁴⁵Y, ²¹⁵N and ⁴⁸⁰V deletions in the spike of JN.1 variant was also found. Thus, few extra deletions in the spike were compensated by the insertion of ¹⁷MPLF sequence in JN.1 and might be responsible for higher transmission.



Figure 1: Demonstration of new spike protein insertion (A) and deletion (B) mutants of omicron JN.1 variant and omicron XBB.1.5.103 subvariant respectively. The data compared with standard Wuhan coronavirus (accession no. NC_045512.2)

TM 1_00010554_008_01_11_0000	teagtgtgttaatettacaaceagaaeteaattaceeeetgeatacae	21648
TD 1 1-08916767-088-17-11-2023	traat at t =============================	21437
PT 1 5 1_00016447_008_13_11_2023	taatatatta taataa taatata taataa taataa taataa	21406
/PD 1 5 102-00012012-21-11-2023	toagtotte-MDI Personal attaitagaattaaa	21400
VBB 1 16 22-00017017-22-11-2023	toagtgtgttmruraltottataacagaactcaaurrtoatacac	21493
ND 1_00017330_008_36 10 2023	toagtgtgtt	21500
N 5 1 1_00017256_058_10.2025	toagtgtgttaltottataacagaactcaatoatacac	21500
0.3.1.1.1-00013204-03A-10-10-2023	*********	**.)0u
-Wuhan-NC 045512-2019	tteaactcaqqacttqttettacctttettttecaatqttacttqqttccatqctataca	21768
N.1-0R919554-USA-21-11-2023	tttaaeteaggaettgttettaeetttettteeaatgttaettggtteeatgetate	21708
D.1.1-OR916767-USA-17-11-2023	tteaaeteaggaettgttettaeetttettteeaatgttaettggtteeatgetataea	21557
L.1.5.1-OR916447-USA-13-11-2023	tteaaeteaggaettgttettaeetttettteeaatgttaettggtteeatgetataea	21606
BB.1.5.103-0R917012-21-11-2023	tteaaeteaggaettgttettaeetttetttteeaatgttaettggtteeatgetataea	21615
BB.1.16.23-0R917017-22-11-2023	tteaaeteaggaettgttettaeetttettteeaatgttaettggtteeatgetataea	21678
V.1-OR817238-USA-26.10.2023	tteaaeteatgaettgttettaeetttetttteeaatgttaettggtteeatgetataea	21700
G.5.1.1-OR813264-USA-10-10-2023	tteaacteatgacttgttettacctttetttteeaatgttacttggttecatgetataca	21700
-Wuhan-NC 045512-2019	tgtetetgggaccaatggtactaagaggtttgataaccetgteetaceatttaatgatgg	21828
N.1-08919554-USA-21-11-2023	HVtetgggaccaatggtactaagaggtttgataaccetgteetaccatttaatgatgg	21766
D.1.1-OR916767-USA-17-11-2023	tgtetetgggaccaatggtactaagaggtttgataaceetgeeetaeeatttaatgatgg	21617
L.1.5.1-OR916447-USA-13-11-2023	tgtetetgggaeeaatggtaetaagaggtttgataaceetgeeetaeeatttaatgatgg	21666
BB.1.5.103-OR917012-21-11-2023	tgtetetgggaeeaatggtaetaagaggtttgataaceetgeeetaeeatttaatgatgg	21675
BB.1.16.23-OR917017-22-11-2023	tgtetetgggaeeaatggtaetaagaggtttgataaceetgeeetaeeatttaatgatgg	21738
V.1-OR817238-USA-26.10.2023	tgtetetgggaeeaatggtaetaagaggtttgataaceetgeeetaeeatttaatgatgg	21760
G.5.1.1-OR813264-USA-10-10-2023	tgtetetgggaeeaatggtaetaagaggtttgataaeeetgeeetaeeatttaatgatgg	21760
-Wuhan-NC_045512-2019	agtctgtgaatttcaattttgtaatgatccatttttgggtgtttattaccacaaaaacaa	22008
N.1-0R919554-USA-21-11-2023	agtctgtgaatttcaattttgtaatgatccatttttggatgtttaccacaaaaacaa	21943
TD.1.1-OR916767-USA-17-11-2023	agtctgtgaatttcaattttgtaatgatccatttttggatgtt=¥-taccaaaaaaacaa	21794
L.1.5.1-OR916447-USA-13-11-2023	agyctgtgaatttcaattttgtaatgatccatttttggatgtttaccaaaaaaacaa	21843
BB.1.5.103-OR917012-21-11-2023	agtotgtgaatttcaattttgtaatgatccatttttggatgtttaccaaaaaaaacaa	21852
KBB.1.16.23-OR917017-22-11-2023	<u>agtotgtgaatttcaattttgtaatgatccatttttggatgtt===taccaaaaaaacaa</u>	21915
KBB.1.16.23-0R917017-22-11-2023 HV.1-0R817238-USA-26.10.2023 EG.5.1.1-0R813264-USA-10-10-2023	agtotgtgaatttcaattttgtaatgatccatttttgqatgtttaccaasaasaacaa agtotgtgaatttcaattttgtaatgatccatttttgqatgttY-taccaasaasaacaa agtotgtgaatttcaattttgtaatgatccatttttgqatgttLaccaasaasaacaa agtotgtgaatttcaattttagtaatgatccatttttgqatgtt	21915 21937 21937
KBB.1.16.23-OR917017-22-11-2023 HV.1-OR817238-USA-26.10.2023 2G.5.1.1-OR813264-USA-10-10-2023	agtotqtgaatttcaattttqtaatgatccatttttqqatgtttaccaaaaaaacaaaagtotqtgaatttcaattttgtaatgatccatttttqqatgtt-Y-taccaaaaaaacaaaagtotqtgaatttcaattttgtaatgatccatttttqqatgtttaccaaaaaaacaaaagtotqtgaatttcaattttgtaatgatccattttttqatgtttaccaaaaaaacaa	21915 21937 21937
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<pre>KBB.1.16.23-0R917017-22-11-2023 tv.1-0R817238-U8A-26.10.2023 2G.5.1.1-0R813264-U8A-10-10-2023 B=Wuhan=NC_045512-2019 JD.1-0R919554-U8A-21-11-2023 JD.1.1-0R916767-U8A-21-11-2023</pre>	agtotgtgaatttoaattttgtaatgatcoatttttgqatgt+taccaasaaacaa agtotgtgaatttoaattttgtaatgatcoatttttgqatgt+Y-taccaasaaacaa agtotgtgaatttoaatttgtaatgatcoatttttgqatgt+taccaasaaacaa atatgteteteageettttettatggaeettgaaggaaaacagggtaattteaaaatet atatgteteteageettttettatggaeettgaaggaaaacagggtaattteaaaatet atatgteteteageettttettatggaeettgaaggaaaacagggtaattteaaaatet atatgteteteageettttettatggaeettgaaggaaaacagggtaattteaaaatet	21915 21937 21937 22937 2212 2206 2191
<pre>KBB.1.16.23-00917017-22-11-2023 tv.1-00817238-USA-26.10.2023 cg.5.1.1-00813264-USA-10-10-2023 B=Wuhan=NC_045512-2019 TM.1-008919554-USA-21-11-2023 TD.1.1-008916767-USA-17-11-2023 FL.1.5.1-00891647-USA-13-11-2023</pre>	attottgaatttoattttttaatgatcoatttttgatgttaccaasaaacaa agtotgtgaatttoattttgtaatgatcoatttttggatgt-Y-taccaasaaaacaa agtotgtgaatttoatttotatgtaatgatcoatttttggatgt	21915 21937 21937 22937 2212 2206 2191 2196
BB.1.16.23-OR917017-22-11-2023 IV.1-OR817238-USA-26.10.2023 G.5.1.1-OR813264-USA-10-10-2023 B-Wuhan-NC_045512-2019 IN.1-OR919554-USA-21-11-2023 ID.1.1-OR916554-USA-21-11-2023 FL.1.5.1-OR916447-USA-13-11-2023 GB.1.5.107-OR917012-21-11-2023	attotstgaatttoaatttstatgatooattttstgatgttaccaasaaacaa agtotstgaatttoatttstatgatooattttstgatgt-Y-taccaasaaaacaa agtotstgaatttoatttstatgatooattttstgatgt	21915 21937 21937 22937 2204 2191 2194 2195
<pre>EBB.1.16.23-00917017-22-11-2023 tv.1-0R817238-U8A-26.10.2023 CG.5.1.1-0R813264-U8A-10-10-2023 E=Wuhan=NC_045512-2019 JD.1-0R919554-U8A-21-11-2023 JD.1.1-0R916767-U8A-17-11-2023 FL.1.5.1-0R916447-U8A-13-11-2023 FL.1.5.10-00917012-22-11-2023</pre>	agtotgtgaatttoaattttgtaatgatocatttttgqatgt+taccaasaasacaa agtotgtgaatttoaattttgtaatgatocatttttgqatgt+Y-taccaasaaaacaa agtotgtgaatttoaatttgtaatgatocatttttgqatgt+	21915 21937 21937 22937 2206 2191 2196 2195 2195 2203
<pre>KBB.1.16.23-0R917017-22-11-2023 iV.1-0R817238-U8A-26.10.2023 iG.5.1.1-0R813264-U8A-10-10-2023 B=Wuhan=NC 045512-2019 IN.1-0R919554-USA-21-11-2023 ID.1.1-0R916767-USA-17-11-2023 PL.1.5.1-0R916447-USA-13-11-2023 KBB.1.5.103-0R917012-22-11-2023 KBB.1.16.23-0R917017-22-11-2023 KBB.1.16.23-0R917017-22-11-2023</pre>	attottgaatttoatttttttaatgatootttttgatgttaccaasaaacaa agtotgtgaatttoattttgtaatgatootttttgatgt	221915 21937 21937 21937 2204 2193 2195 2205 2205 2205 2205
BB.1.16.23-00917017-22-11-2023 IV.1-0R817238-USA-26.10.2023 3G.5.1.1-0R813264-USA-10-10-2023 B=Wuhan=NC_045512-2019 ID.1-0R919554-USA-21-11-2023 ID.1.1-0R916767-USA-13-11-2023 PL.1.5.1-0R916447-USA-13-11-2023 CBB.1.5.1-03-00917012-22-11-2023 IV.1-0R817238-USA-26.10.2023 EC.5.1.1-0R813264-USA-10-10-2023	agtotgtgaatttoaattttgtaatgatocatttttgqatgttaccaasaaacaa agtotgtgaatttoaattttgtaatgatocatttttgqatgt-Y-taccaasaaacaa agtotgtgaatttoaatttgtaatgatocatttttgqatgt	21915 21937 21937 22937 22937 2294 2195 2205 2205 2205 2205
<pre>RBB.1.16.23-00917017-22-11-2023 WV.1-0R817238-U8A-26.10.2023 GG.5.1.1-0R813264-U8A-10-10-2023 B=Wuhan=NC_045512-2019 JD.1-0R919554-U8A-21-11-2023 JD.1.1-0R916767-U8A-17-11-2023 PL.1.5.1-0R916447-U5A-13-11-2023 KBB.1.16.271-0R917012-22-11-2023 KBB.1.5.1-028916447-U5A-13-11-2023 KBB.1.16.271-0R917012-22-11-2023 KD.1.5.1-0R813238-U5A-26.10.2023 EC.5.1.1-0R813264-U5A-10-10-2023 B=Wuhan=NC_045512-2019</pre>	agtotgtgaatttoaattttgtaatgatocatttttgqatgttaccaasaaacaa agtotgtgaatttoaattttgtaatgatocatttttgqatgt-Y-taccaasaaacaa agtotgtgaatttoaatttgtaatgatocatttttgqatgt	21915 21937 21937 21937 21937 21937 21937 2193 2194 2195 2205 2205 2205 2205 2205 2205
BB.1.16.23-00917017-22-11-2023 IV.1-0R817238-USA-26.10.2023 G.5.1.1-0R813264-USA-10-10-2023 B-Wuhan-NC 045512-2019 IN.1-0R919554-USA-21-11-2023 ID.1.1-0R916767-0ISA-13-11-2023 ID.1.5.1-0R916447-USA-13-11-2023 IR.1.5.103-0R917012-21-11-2023 IR.1.6.23-0R917012-22-11-2023 IV.1-0R817238-USA-26.10.2023 EG.5.1.1-0R813264-USA-10-10-2023 B-Wuhan-NC 045512-2019 IN.1-0R919554-USA-21-11-2023	attgteteteageetttettatggaeettgaaggaaaacagggtaattteaaaatet atatgteteteageetttettatggaeettgaaggaaaacagggtaattteaaaatet atatgteteteageetttettatggaeettgaaggaaaacagggtaattteaaaatet atatgteteteageetttettatggaeettgaaggaaaacagggtaattteaaaatet atatgteteteageetttettatggaeettgaaggaaaacagggtaattteaaaatet atatgteteteageetttettatggaeettgaaggaaaacagggtaattteaaaatet atatgteteteageetttettatggaeettgaaggaaaacagggtaattteaaaatet atatgteteteageetttettatggaeettgaaggaaaacagggtaattteaaaatet atatgteteteageetttettatggaeettgaaggaaaacagggtaattteaaaatet atatgteteteageetttettatggaeettgaaggaaaacagggtaattteaaaatet atatgteteteageetttettatggaeettgaaggaaaagggtaattteaaaatet atatgteteteageetttettatggaeettgaaggaaaagggtaattteaaaatet atatgteteteageetttettatggaeettgaaggaaaagggtaattteaaaatet atatgteteteageetttettatggaeettgaaggaaaagggtaattteaaaatet atatgteteteageetttettatggaeettgaaggaaaagggtaattteaaaatet atatgteteteageetttettatggaeettgaaggaaaagggtaattteaaaatet atatgteteteagegtttettetatggaeettgaaggaaaagaggtaattteaaaatet	21915 21937 21937 22937 22937 2204 2193 2205 2205 2205 2205 2205 2205 2205 220
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BB.1.16.23-0R917017-22-11-2023 IV.1-OR817238-USA-26.10.2023 G.5.1.1-OR813264-USA-10-10-2023 B=Wuhan=NC 045512-2019 ID.1.1-OR91654-USA-21-11-2023 ID.1.1-OR916767-USA-13-11-2023 PL.1.5.1-OR916447-USA-13-11-2023 IV.1-OR817238-USA-26.10.2023 BB.1.16.23-OR917017-22-11-2023 IV.1-OR817238-USA-26.10.2023 BC.5.1.1-OR813264-USA-10-10-2023 B=Wuhan=NC 045512-2019 IN.1-OR919554-USA-21-11-2023 ID.1.1-OR919564-USA-21-11-2023 ID.1.1-OR916567-USA-17-11-2023 ID.1.1-OR916447-USA-13-11-2023 ID.1.1-OR916447-USA-13-11-2023 ID.1.1-OR916447-USA-13-11-2023 ID.1.1-OR916447-USA-13-11-2023 ID.1.1-OR916447-USA-13-11-2023 ID.1.1-OR916447-USA-13-11-2023 ID.1.1-OR916447-USA-13-11-2023 ID.1.1-OR916447-USA-13-11-2023 ID.1.1-OR917012-21-11-2023 ID.1.1-0R91701	atatgteteteageetttettatggaeettgaaggaaaacagggtaattteaaaatet atatgteteteageetttettatggaeettgaaggaaaacagggtaattteaaaatet atatgteteteageetttettatggaeettgaaggaaaacagggtaattteaaaatet atatgteteteageetttettatggaeettgaaggaaaacagggtaattteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteagegtttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteagegtttetetatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteagegtttetetatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteagegtttetetatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteagegtttetetatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteagegtggatteeeteagggtttteggetttagaaeeattggtagattt tattaatttagaeggtgaeteeeteagggtttteggettagaaeeattggtagattt tattaatttagaeggtgatteeeteagggtttteggettagaaeeattggtagattt	21915 21937 21937 21937 21937 21937 2193 2194 2195 2203 2205 2205 2205 2205 2205 2205 220
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<pre>RBB.1.16.23-0R917017-22-11-2023 RV.1-0R817238-U8A-26.10.2023 EG.5.1.1-0R813264-U8A-10-10-2023 B=Wuhan=NC_045512-2019 JN.1-0R919554-U5A-21-11-2023 JD.1.1-0R916767-U5A-17-11-2023 JD.1.1-0R916767-U5A-13-11-2023 KBB.1.5.103-0R917012-221-11-2023 RV.1-0R817238-U5A-26.18.2023 EG.5.1.1-0R91854-U5A-21-11-2023 JD.1.1-0R919554-U5A-21-11-2023 FL.1.5.1-0R916447-U5A-13-11-2023 FL.1.5.1-0R916447-U5A-13-11-2023 FL.1.5.1-0R916447-U5A-13-11-2023 FL.1.5.1-0R916447-U5A-13-11-2023 FL.1.5.1-0R916447-U5A-13-11-2023 KBB.1.1.6.23-0R917017-22-11-2023 EG.5.1.1-0R91654-U5A-26.10.2023 EC.5.1.1-0R916447-U5A-13-11-2023 KBB.1.5.103-0R917017-22-11-2023 EC.5.1.1-0R91654-U5A-20-10-2023 EC.5.1.1-0R916767-U5A-17-11-2023 KDB.1.1-0R919554-U5A-21-11-2023 KDJ.1-0R919554-U5A-21-11-2023 KDJ.1-0R919554-U5A-21-11-2023 KDB.1.5.103-0R917012-21-11-2023 KDB.1.5.103-0R917012-21-11-2023 KDB.1.5.103-0R917017-22-11-2023 KDB.1.16.23-0R917017-22-11-2023 KDB.1.16</pre>	atatgteteteageetttettatggaeettgaaggaaaaeagggtaattteaaaatet atatgteteteageetttettatggaeettgaaggaaaaeagggtaattteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaattteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageettteeteaggettttoggettagaaeeattggtagattt tataatttagtegtgatteeeteagggtttteggettagaaeeattggtagattt tattaatttagagegtgatteeeteagggtttteggettagaaeeattggtagattt tattaatttagagegtgateeeteagggtttteggettagaaeeattggtagattt tattaatttagagegtgateeeteagggtttteggettagaaeeattggtagattt tattaatttagagegtgateeeteagggtttteggettagaaeeattggtagattt tattaatttagagegtgateeeteagggtttteggettagaaeeattggtagattt tattaatttagagegtgateeeteaggttttteggettagaaeeattggtagattt tattaatttagaeggtgateeeteaggttttteggettagaaeeattggtagattt tattaattagaeggtgateeeteaggtttteggettagaaeeattggtagtttta aaetgaaatetateaggeeggtaaeaaaeettgtaatggtgtgeaggteetaattgtta aaetgaaatetateaggeeggtaaeaaaeettgtaatggtgtgeaggteetaattgtta aaetgaaatetateaggeeggtaaeaaaeettgtaatggtgtgeaggteetaattgtta aaetgaaatetateaggeeggtaaeaaaeettgtaatggtgtgeaggteetaattgtta aaetgaaatetateaggeeggtaaeaaaeettgtaatggtgtgeaggteetaattgtta aaetgaaatetateaggeeggtaaeaaaeettgtaatggtgtgeaggteetaattgtta aaetgaaatetateaggeeggtaaeaaaeettgtaatggtgtgeaggteetaattgtta	21915 21937 21937 21937 22936 21937 22936 2193 2205 2205 2205 2205 2207 2217 2217 2217 2217 2217 2217 2217
<pre>KBB.1.16.23-0R917017-22-11-2023 WV.1-0R817238-USA-26.10.2023 EG.5.1.1-0R813264-USA-10.10-2023 B-Wuhan-NC_045512-2019 JD.1.1-0R919554-USA-21-11-2023 FL.1.5.1-0R916447-USA-13-11-2023 KBB.1.16.23-0R917017-22-11-2023 WV.1-0R817238-USA-26.10.2023 EC.5.1.1-0R919554-USA-21-11-2023 KBB.1.6.23-0R917017-22-11-2023 FL.1.5.1-0R919554-USA-21-11-2023 FL.1.5.1-0R919554-USA-21-11-2023 FL.1.5.1-0R919554-USA-21-11-2023 FL.1.5.1-0R919554-USA-21-11-2023 KBB.1.5.103-0R917017-22-11-2023 KBB.1.5.103-0R917017-22-11-2023 KBB.1.5.103-0R917017-22-11-2023 KBB.1.1-0R919554-USA-26.10.2023 EC.5.1.1-0R919554-USA-27-11-2023 KBB.1.5.103-0R917017-22-11-2023 KBB.1.5.103-0R917017-22-11-2023 KBB.1.5.103-0R917017-22-11-2023 KBB.1.5.103-0R917017-22-11-2023 KBB.1.5.103-0R917017-22-11-2023 KBB.1.5.103-0R917017-22-11-2023 KBB.1.5.103-0R917017-22-11-2023 KBB.1.5.103-0R917017-22-11-2023 KBB.1.6.23-0R917017-22-11-2023 KBB.1.6.23-0R917017-22-11-2023 KBB.1.6.23-0R917017-22-11-2023 KBB.1.6.23-0R917017-22-11-2023 KBB.1.16.23-0R917017-22-11-2023 KBB.1.16.23-0R917017-22-11-2023 KBB.1.16.23-0R917017-22-11-2023 KBB.1.16.23-0R917017-22-10-2023</pre>	atatgteteteageetttettatggaeettgaaggaaaaeagggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaaeagggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageetttettatggaeettgaaggaaaagaggtaatteaaaatet atatgteteteageettteeteeteagggtttteggettagaaeeattggtagattt tataattagagegtgateteeeteagggtttteggettagaaeeattggtagattt tataattagagegtgateteeeteagggtttteggettagaaeeattggtagattt tataattagagegtgateteeeteagggtttteggettagaaeeattggtagattt tataattagagegtgateteeeteagggtttteggettagaaeeattggtagattt tataattagagegtgateteeeteagggtttteggettagaaeeattggtagattt tataattagagegtgateteeeteagggtttteggettagaaeeattggtagattt tataattagaeggtgateteeeteagggtttteggettagaaeeattggtagttta aaetgaaatetateaggeeggtaaeaaaeettgtaatggtgtgeaggteetaattgtta aaetgaaatetateaggeeggtaaeaaaeettgtaatggtgttgeaggteetaattgtta aaetgaaatetateaggeeggtaaeaaaeettgtaatggtgttgeaggteetaattgtta aaetgaaatetateaggeeggtaaeaaaeettgtaatggtgttgeaggteetaattgtta	21915 21937 21937 21937 21937 2295 2205 2205 2205 2205 2205 2205 2207 2217 2217 2217 2217 2217 2217 2217

Figure 2: Multi-alignment of genomes of new corona virus variants with deletion and insertion in the spike as shown in figure-1. We confirmed the all deletions (²⁴LPP, ⁶⁹HV, ¹⁴⁵Y, ²¹¹N and ⁴⁸³V) in the spike during genome wide search. The ¹⁷ MPLF insertion was found in the spike of omicron JN.1 subvariant only.

The previously reported the XBB.1.5 lineage GGA=TGA termination codon mutation of ORF8 gene was found in XBB.1.5.103 and XBB.1.16.23 as expected. But such mutation was also appeared in FL.1.5.1, HV.1, EG.5.1.1 and JD.1.1. Table-1 showed the main lineage (XBB.1) from where these new subvariant were derived. This data clearly demonstrated their common source lineage was XBB.1 and too many new names in the omicron sub-lineages spoiled the game. Thus, recent

omicron coronavirus nomenclature was exacerbated without reason. As for example, FL.1.5.1 and EG.5 are essentially same and similarly JN.1 and BA.2.86.1 are very same with one spike mutation difference. We also found that FL.1.5.1 subvariant had a deletion in the ORF7b-ORF8 boundary that completely removed the ATG codon of ORF8 gene (figure-3). In figure-4, we showed the few new amino acid changes at the RBD of spike including N501Y mutation in those new variants of XBB.1 descendant.

New name	Source	Old name	Accession number
JN.1	BA.2.86	BA.2.86 + L455S Spike	OR919554
XBB.1.5.103	XBB.1.5	XBB.1.5 + E150Q, N181D,	OR917012
		F452L+ ¹⁷⁶ EGKEG Del Spike	
XBB.1.16.23	XBB.1.16	XBB.1.16 + P486S	OR917017
XBB.1.16	XBB.1	XBB.1 + Y145 Del + 15	OR871702
		spike mutations	
XBB.1.5	XBB.1	XBB.1 + F486P Spike	OQ816854
XBB.1	XBB	XBB + G252V Spike	OR741908
XBB	BJ.1+ BM.1.1.1	BJ.1 =BA.2.10.1	OQ080316
		BM.1.1.1=BA.2.75.3.1.1.1	OQ166287
JD.1.1	XBB.1.5.102	XBB.1.5.102.1.1.1	OR916767
FL.1.5.1	XBB.1.9.1	XBB.1.9.1.1.5.1	OR916447
HV.1	EG.5 or XBB.1.9.2.5	XBB.1.9.2.5.1.6.1	OR817238
EG.5.1.1	XBB.1.9.2	XBB.1.9.2.5.1.1	OR813264
BA.1	B.1.1.529	B.1.1.529.1	OM542730
BN.1	BA.2.75	B.1.1.529.2.75.1	OQ114394
BF.7	BA.5.2	B.1.1.529.5.2.1.7	OP440319
BQ.1	BA.5.3	B.1.1.529.5.3.1.1.1.1.1	OQ392531

Table 1: Correct Nomenclature of New Omicron Variants with Recent Higher Transmission

Variant Accession Date	ORF7a gene region	
B=Wuhan=NC_045512=2019	geaatagtgtttataacactttgetteacacteaaaagaaagacagaatg <mark>at</mark> tgaacttt	27768
JN.1-OR919554-USA-21-11-2023	geaatagtgtttataacactttgetteacaeteaaaagaaagacaga <mark>atgaa</mark> ttgaacttt	27697
JD.1.1-0R916767-USA-17-11-2023	geaatagtgtttataacaetttgetteacaeteaaaagaaagacagaatgattgaaettt	27554
FL.1.5.1-OR916447-USA-13-11-2023	geaatagtgtttataaeaetttgetteaeaeteaaaagaaag	27603
XBB.1.5.103-0R917012-21-11-2023	geaatagtgtttataacactttgetteacactcaaaagaaagacagaatgattgaacttt	27597
XBB.1.16.23-0R917017-22-11-2023	geaatagtgtttataacactttgetteacactcaaaagaaagacagaatgaatgaacttt	27675
HV.1-OR817238-USA-26.10.2023	geaatagtgtttataaeaetttgetteaeaeteaaaagaaag	27697
EG.5.1.1-OR813264-USA-10-10-2023	gcaatagtgtttataacactttgcttcacacttaaaagaaag	27697

	TGA ORE74	ATG ORF7b
B-Wuhan-NC 045512-2019	cattaattgacttetatttgtgetttttageetttetgetatteettgttttaattatge	27828
JN.1-0R919554-USA-21-11-2023	cattaattgacttetatttgtgetttttageetttetgttaeteettgttttaattatge	27757
JD.1.1-OR916767-USA-17-11-2023	cattaattgacttetatttgtgetttttageetttetgttatteettgttttaattatge	27614
FL.1.5.1-OR916447-USA-13-11-2023	cattaattgacttetatttgtgetttttageetttetgttatteettgttttaattatge	27663
XBB.1.5.103-0R917012-21-11-2023	cattaattgacttetatttgtgetttttageetttetgttatteettgttttaattatge	27657
XBB.1.16.23-0R917017-22-11-2023	cattaattgacttetatttgtgetttttageetttetgttatteettgttttaattatge	27735
HV.1-OR817238-USA-26.10.2023	cattaattgacttetatttgtgetttttageetttetgttatteettgttttaattatge	27757
EG.5.1.1-OR813264-USA-10-10-2023	cattaattgacttetatttgtgetttttageetttetgttatteettgttttaattatge	27757

B-Wuhan-NC 045512-2019	ttattatettttggtteteaettgaaetgeaagateataatgaaaettgteaegeetaaa	27888
JN.1-0R919554-USA-21-11-2023	ttattatettttggtteteaettgaaetgeaagateataatgaaaettgteaegeetaaa	27817
JD.1.1-OR916767-USA-17-11-2023	ttattatettttggtteteaettgaactgcaagateataatgaaacttgtcacgeetaaa	27674
FL.1.5.1-OR916447-USA-13-11-2023	ttattatettttggtteteaettgaaetgeaagateataatgaaaettgteaegeeta	27721
XBB.1.5.103-0R917012-21-11-2023	ttattatettttggtteteaettgaactgcaagateataatgaaaettggcacgeetaaa	27717
XBB.1.16.23-0R917017-22-11-2023	ttattatettttggtteteaettgaaetgeaagateataatgaaaettgteaegeetaaa	27795
HV.1-OR817238-USA-26.10.2023	ttattatettttggtteteaettgaaetgeaagateataatgaaaettgteaegeetaaa	27817
EG.5.1.1-OR813264-USA-10-10-2023	ttattatettttggtteteeettgaaetgeaagateataatgaaaettgteaegeetaaa	27817

	GGA=TGA mutation TAA OF	F7b
B-Wuhan-NC_045512-2019	egaacatgaaatttettgttttettaggaateateaeaaetgtagetgeattteaeeaag	27948
JN.1-0R919554-USA-21-11-2023	egaacatgaaatttettgttttettaggaateateaeaaetgtagetgeattteaeeaag	27877
JD.1.1-OR916767-USA-17-11-2023	egaacatgaaatttettgttttettatgaateateacaactgtagetgeattteaceaag	27734
FL.1.5.1-OR916447-USA-13-11-2023	atgaateateacaactgtagetgeattteaceaag	27756
XBB.1.5.103-0R917012-21-11-2023	egaacatgaaatttettgttttettatgaatcatcacaactgtagetgeattteaccaag	27777
XBB.1.16.23-0R917017-22-11-2023	egaacatgaaatttettgttttettatgaatcatcacaactgtagetgeatttcaccaag	27855
HV.1-OR817238-USA-26.10.2023	egaacatgaaatttettgttttettatgaateateacaactgtagetgeattteaceaag	27877
EG.5.1.1-OR813264-USA-10-10-2023	egaacatgaaatttettgttttettatgaatcatcacaactgtagetgeatttcaccaag	27877
	ATG ORF8	
	Early termination of ORF8 at 8th codon r	nutation

Figure 3: Demonstration of ORF8 gene termination codon mutation at 8th codon in XBB.1.5.103 as well as XBB.1.1.6.23, JD.1.1, HV.1, EG5.1.1 as previously described in all XBB.1.5 variants (Chakraborty AK. Cohesive J Microbiol Infect Dis. 2023; 6(5): CJMI.000646).



Figure 4: Demonstration of some unique new amino acid mutations (442H=P449H, 449W=L456W, 474K=N485K,480K= A488K etc) in the Receptor Binding Domain (RBD) of JN.1 variant.

Then, we want to see the database penetration of insertion and deletion spike mutants as discussed above. For that we made insertion-oligo and deletion-oligo at the insertion and deletion boundaries. The JN.1-MPLF-insertion-oligo is: 5'-gtc tct agt cag tgt gtc atg ccg ctg ttt aat ctt ata act aca act caa-3'. The XBB.1.5.103-EGKEG-Deletion oligo: 5'-cag cct ttt ctt atg gac ctt gat ttc aaa aat ctt agg gaa-3'. The BLASTN search detected about >3895 sequences for insertion-oligo for JN.1 variant on dated 1.1.2024 (figure-5) and >75 sequences for deletion oligo for deletion oligo for XBB.1.5.103 variant (figure-6). It was found that JN.1 sequences are more recent (November-December, 2023) than XBB.1.5.103 sequences still JN.1 sequences are progressing fast in the America and Europe (figure-7 and figure-8). However, last minute NCBI Virus Database search (10.1.2024) with JN.1-MPLF-oligo indicated more than 4984 JN.1 and BA.2.86.1 sequences which was 27% increase than we detected in 9 days ago. The Indian newspaper (The times of India, 20.12.2023, 31.12.2023, 9.1.2024) reported the spread (~500 infections and three deaths with co-morbilities) of such JN.1 coronavirus in India in the province of Goa, Tamil Nadu, Karnataka, Maharashtra and West Bengal. The British Newspaper indicated every twenty-four person, one JN.1 affected person could be found in England and Scotland (www. bloomberg.com 21st December, 2023). The USA was severely affected too as described by CDC (www.cdc.gov/respiratory-virus-updates 22th December, 2023).

	Description	Scientific Name	Max Score	Total Score	Query Cover	E value	Per. Ident	Acc. Len	Accession
	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/USA/2368605/2023 ORF1ab pol	Severe acute res	93.5	93.5	100%	2e-15	100.00%	29649	OR906019.1
✓	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/USA/2368603/2023 ORF1ab pol	Severe acute res	93.5	93.5	100%	2e-15	100.00%	29649	OR906017.1
~	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/USA/2368366/2023 ORF1ab pol	Severe acute res	93.5	93.5	100%	2e-15	100.00%	29649	OR906008.1
✓	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/USA/2367509/2023 ORF1ab pol	Severe acute res	93.5	93.5	100%	2e-15	100.00%	29649	OR905970.1
~	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/USA/2367130/2023 ORF1ab pol	Severe acute res	93.5	93.5	100%	2e-15	100.00%	29649	OR905965.1
✓	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/USA/2366815/2023 ORF1ab pol	Severe acute res	93.5	93.5	100%	2e-15	100.00%	29649	OR905961.1
~	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/USA/2366814/2023 ORF1ab pol	Severe acute res	93.5	93.5	100%	2e-15	100.00%	29649	OR905960.1
✓	Severe acute respiratory syndrome coronavirus 2 genome assembly, chromosome: 1	Severe acute res	93.5	93.5	100%	2e-15	100.00%	29850	<u>OY855842.1</u>
✓	Severe acute respiratory syndrome coronavirus 2 genome assembly, chromosome: 1	Severe acute res	93.5	93.5	100%	2e-15	100.00%	29850	<u>OY855833.1</u>
✓	Severe acute respiratory syndrome coronavirus 2 genome assembly, chromosome: 1	Severe acute res	93.5	93.5	100%	2e-15	100.00%	29850	<u>OY855825.1</u>
✓	Severe acute respiratory syndrome coronavirus 2 genome assembly, chromosome: 1	Severe acute res	93.5	93.5	100%	2e-15	100.00%	29850	<u>OY855814.1</u>
<	Severe acute respiratory syndrome coronavirus 2 genome assembly, chromosome: 1	Severe acute res	93.5	93.5	100%	2e-15	100.00%	29826	<u>OY855617.</u>
~	Severe acute respiratory syndrome coronavirus 2 genome assembly, chromosome: 1	Severe acute res	93.5	93.5	100%	2e-15	100.00%	29873	<u>OY855616.</u>

Figure 5: BlastN search to demonstrate the huge spread (>500) of spike MPLF insertion omicron Coronavirus JN.1 variant sequences. JN.1-MPLF-insertion-oligo: 5'-gtc tct agt cag tgt gtc atg ccg ctg ttt aat ctt ata act aca act caa-3'.

	Description	Scientific Name	Max Score	Total Score	Query Cover	E value	Per. Ident	Acc. Len	Accession
	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/USA/ND-USAFSAM-S21586/2023	Severe acute res	78.7	78.7	100%	3e-11	100.00%	29739	OR886861.1
	Severe acute respiratory syndrome coronavirus 2 genome assembly, chromosome: 1	Severe acute res	78.7	78.7	100%	3e-11	100.00%	29858	<u>OY790445.1</u>
	Severe acute respiratory syndrome coronavirus 2 genome assembly, chromosome: 1	Severe acute res	78.7	78.7	100%	3e-11	100.00%	29858	<u>OY788425.1</u>
	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/USA/GA-GPHL-1018/2023 ORF1	Severe acute res	78.7	78.7	100%	3e-11	100.00%	29741	OR838630.1
	Severe acute respiratory syndrome coronavirus 2 genome assembly, chromosome: 1	Severe acute res	78.7	78.7	100%	3e-11	100.00%	29858	<u>OY783551.1</u>
	Severe acute respiratory syndrome coronavirus 2 genome assembly, chromosome: 1	Severe acute res	78.7	78.7	100%	3e-11	100.00%	29858	<u>OY780265.1</u>
	Severe acute respiratory syndrome coronavirus 2 genome assembly, chromosome: 1	Severe acute res	78.7	78.7	100%	3e-11	100.00%	29858	<u>OY779010.1</u>
	Severe acute respiratory syndrome coronavirus 2 genome assembly, chromosome: 1	Severe acute res	78.7	78.7	100%	3e-11	100.00%	29823	<u>OY777884.1</u>
	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/USA/ND-USAFSAM-S21543/2023	Severe acute res	78.7	78.7	100%	3e-11	100.00%	29740	OR825084.1
	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/USA/ND-USAFSAM-S21542/2023	Severe acute res	78.7	78.7	100%	3e-11	100.00%	29739	OR825083.1
	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/USA/CT-DPH-1177255001/2023	Severe acute res	78.7	78.7	100%	3e-11	100.00%	29633	OR791623.1
	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/USA/VT-23-008705-WGS-02/2023	Severe acute res	78.7	78.7	100%	3e-11	100.00%	29691	OR783752.1
	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/USA/NY-PRL-231020_81A01/202	Severe acute res	78.7	78.7	100%	3e-11	100.00%	29738	OR710511.1
	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/USA/CA-CDPH-500125630/2023	Severe acute res	78.7	78.7	100%	3e-11	100.00%	29756	OR703517.1
	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/USA/CA-CDPH-500125112/2023	Severe acute res	78.7	78.7	100%	3e-11	100.00%	29756	OR703431.1
	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/USA/NJ-PHEL-V23016091/2023	Severe acute res	78.7	78.7	100%	3e-11	100.00%	29634	OR689681.1
~	Severe acute respiratory syndrome coronavirus 2 isolate SARS-CoV-2/human/USA/WA-PHL-034887/2023 ORF1	Severe acute res	78.7	78.7	100%	3e-11	100.00%	29676	OR680213.1

Figure 6: Blast search to demonstrate penetration of ¹⁸⁴EGKQG spike deletion variant of omicron coronavirus XBB.1.5.103 sequences in the database (>75). XBB.1.5.103-EGKQG-oligo: 5'-cag cct ttt ctt atg gac ctt gat ttc aaa aat ctt agg gaa-3'.

Variant/Accession/Date/Country	S gene region	Position
B-Wuhan-NC 045512-2019	tcagtgtgttMPLFaatcttacaaccagaactcaattaccccctgcatacac	21648
0Y854261-20-11-2023-Denmark	tcagtgtgtcatgccgctgtttaatcttataactacaactcaatcatacac	21642
OY855842-20-11-2023-Denmark	tcagtgtgtcatgccgctgtttaatcttataactacaactcaatcatacac	21642
0Y855585-20-11-2023-Denmark	tcagtgtgtcatgccgctgtttaatcttataactacaactcaatcatacac	21642
OR906019-28-11-2023-USA	tcagtgtgtcatgccgctgtttaatcttataactacaactcaaLPPtcatacac	21588
OR882520-8-11-2023-USA	tcagtgtgtcatgccgctgtttaatcttataactacaactcaatcatacac	21595
OR862048-3-11-2023-USA	tcagtgtgtcatgccgctgtttaatcttataactacaactcaatcatacac	21540
OR864490-9-11-2023-USA	tcagtgtgtcatgccgctgtttaatcttataactacaactcaatcatacac	21570
JN.1-OR919554-USA-21-11-2023	tcagtgtgtcatgccgctgtttaatcttataactacaactcaatcatacac	21592
JD.1.1-OR916767-USA-17-11-2023	tcagtgtgtttcatacat	21437
FL.1.5.1-OR916447-USA-13-11-2023	tcagtgtgtttcatacac	21486
XBB.1.5.103-OR917012-21-11-2023	tcagtgtgttMPLFaatcttataaccagaactcaaLPPtcatacac	21495
XBB.1.16.23-OR917017-22-11-2023	tcagtgtgtttcatacac	21558
HV.1-OR817238-USA-26.10.2023	tcagtgtgtttcatacac	21580
EG.5.1.1-OR813264-USA-10-10-2023	tcagtgtgtttcatacac	21580

Figure 7: Genome-wide search of more spike 17MPLF insertion mutants and multi-alignment. It was found that Denmark and USA had high hit for mutant coronavirus. The 24LPP deletion was rampant in all omicron variants.

Variant /Accession /Date /Country	Snike protein region	Position
P When NG 045513 2010		22120
B-wunan-NC_045512-2019	atatgteteteageettttettatggaeettgaaggaaaacagggtaattteaaaaatet	22128
OY779010-Denmark-4.9.2023	atatgtctctcagccttttcttatggacctt <mark>EGKQG</mark> g atttcaaaaatct	22092
0Y854261-20-11-2023-Denmark	atatgtctctcagccttttcttatggaccttgaaggaaaacagggtaatttcaaaaatct	22113
0Y855842-20-11-2023-Denmark	atatgtctctcagccttttcttatggaccttgaaggaaaacagggtaatttcaaaaatct	22113
0Y855585-20-11-2023-Denmark	atatgtctctcagccttttcttatggaccttgaaggaaaacagggtaatttcaaaaatct	22113
OR906019-28-11-2023-USA	atatgtctctcagccttttcttatggaccttgaaggaaaacagggtaatttcaaaaatct	22059
OR882520-8-11-2023-USA	atatgtctctcagccttttcttatggaccttgaaggaaaacagggtaatttcaaaaatct	22066
OR862048-3-11-2023-USA	atatgtctctcagccttttcttatggaccttgaaggaaaacagggtaatttcaaaaatct	22011
OR864490-9-11-2023-USA	atatgtctctcagccttttcttatggaccttgaaggaaaacagggtaatttcaaaaatct	22041
JN.1-OR919554-USA-21-11-2023	atatgtctctcagccttttcttatggaccttgaaggaaaacagggtaatttcaaaaatct	22063
OR617194-USA-14.9.2023	atatgtctctcagccttttcttatggaccttgatttcaaaaatct	22054
OY790445-Denmark-26.6.2023	atatgtctctcagccttttcttatggaccttgatttcaaaaatct	22092
OY741159-England-19.9.2-2023	atatgtctctcagccttttcttatggaccttEGKQGgatttcaaaaatct	22092
XBB.1.5.103-OR917012-21-11-2023	atatgtctctcagccttttcttatggaccttgatttcaaaaatct	21957
OR825084-USA-16.10.2023	atatgtctctcagccttttcttatggaccttgatttcaaaaatct	22038
OR886861-USA-19.10.2023	atatgtctctcagccttttcttatggaccttgatttcaaaaatct	22037
JD.1.1-OR916767-USA-17-11-2023	atatgtctctcagccttttcttatggaccttgaaggaaaagagggtaatttcaaaaatct	21914
FL.1.5.1-OR916447-USA-13-11-2023	atatgtctctcagccttttcttatggaccttgaaggaaaagagggtaatttcaaaaatct	21963
XBB.1.16.23-OR917017-22-11-2023	atatgtctctcagccttttcttatggaccttgtaggaaaagagggtaatttcaaaaatct	22035
HV.1-OR817238-USA-26.10.2023	atatgtctctcagccttttcttatggaccttgaaggaaaagagggtaatttcaaaaatct	22057
EG.5.1.1-OR813264-USA-10-10-2023	atatgtctctcagccttttcttatggaccttgaaggaaaagagggtaatttcaaaaatct	22057

Figure 8: Genome-wide search for spike EGKEG deletion more mutants. It was also distributed in Europe and America. After WHO declared recent spread of coronavirus was mild. So, poor countries including India had stopped further WGS of newly infected coronaviruses.

Then, we wanted to see the spread of ¹⁷MPLF insertion (ATGCCGCTGTTT) among the different BA.2 lineages. It was found that ¹⁷MPLF insertion first appeared in BA.2.86 and BA.2.86.1 subvariants but not in other BA.2 lineages like BA.2.12.1, BA.2.48, BA.2.75 and BA.2.75.10 (figure-9). Further, the spike 69HV deletion was not found in all BA.2 variants (BA.2, BA.2.12, BA.2.48 and BA.2.75) except recently was found in BA.2.86 or BA.2.86.1 lineage as well as new JN.1, JN.2 and JN.3 lineages (figure-9). The mutated JN.1 genome

sequences were authentic and such sequences were done by different famous groups like Howard et al, Freeman et al and Laurin et al (USA) whereas we found JN.1 spread in the 35 US States. Such sequences were also found in Japan (accession nos. BS007751 and BS007749). The partial sequence data was not included in this analysis. In figure-10, we demonstrated the unique spike L455S mutation (L452S in JN.1) suggested in immune escape and higher transmission and such mutation was not detected in BA.2.86 variant.



Figure 9: Demonstration of most spike deletions of JN.1 variant was occurred in BA.2.86 and BA.2.86.1 subvariants. The important ⁶⁹HV deletion was first occurred in B.1.1.7 variant in 2020 and the was found in BA.1, BA.4 and BA.5 omicron variant in 2021. The ⁶⁹HV deletion was not found in all BA.2 variants (BA.2, BA.2.12, BA.2.48 and BA.2.75) except recently was found in BA.2.86 and BA.2.86.1 lineages as well as JN.1, JN.2 and JN.3 lineages. The JN.1 genomes were sequenced by different author and groups: Howard et al, Freeman et al and Laurin et al and Partial sequence data was not included.



Figure 10: Demonstration that the main difference between the spike of BA.2.86 and JN.1 was L455S (S452 in JN.1) mutation. The important spike V445H mutation in JN.1 and BA.2.86 was also shown.

We also demonstrated that only XBB.1.5.103 variant has ¹⁷⁶EGKEG spike deletion but not in other XBB.1.5.1-XBB.1.5.100 subvariants (figure-11). Much of the such data was reported in a book recently published: Chakraborty AK. 2023. Life and Death of COVID-19: Molecular Genetics of SARS-CoV-2. ISBN: 978-1-68576-454-8. Iterative International Publishers, Karnataka, India. First edition, Pp. 119-121. However, part of such data was also published in an Open Access journal: Chakraborty AK. Highly infectious, less pathogenic and antibody resistant omicron XBB.1.5.1-XBB.1.5.39 subvariant coronaviruses

do not produce ORF8 protein due to 8th codon GGA=TGA termination codon mutation. Cohesive J Microbiol Infect Dis. 6(5): CJMI.000648.2023. Doi:10.31031/CJMI.2023.06.000648. We also reported such data in preprint server: Research Square (Preprint), 30th May, 2023. We knew if both 69HV and 24LPP double deletions in the spike, then the variant would be BA.4 or BA.5 omicron variants. But data presented in figure-12 showed that omicron BA.4 and BA.5 spike sequences were very different than JN.1 variant which was selected from BA.2.86 lineage and BA.2.86.1 was also spreading highly.



Figure 11: Demonstration that only XBB.1.5.103 variant has EGKEG deletion but not in XBB.1.5.1-XBB.1.5.100 (Chakraborty AK. 2023. Life and Death of COVID-19: Molecular Genetics of SARS-CoV-2. Book, ISBN: 978-1-68576-454-8. Iterative International Publishers, Karnataka, India. First edition, Pp. 119-121 and Chakraborty AK. Highly infectious, less pathogenic and antibody resistant omicron XBB.1.5.1-XBB.1.5.39 subvariant coronaviruses do not produce ORF8 protein due to 8th codon GGA=TGA termination codon mutation. Cohesive J Microbiol Infect Dis. 6(5): CJMI.000648.2023. Doi:10.31031/CJMI.2023.06.000648) and also deposited in Research Square (Preprint) on 30th May, 2023.

S-BA.5-URO63244-ON658807	tlksftvekgiyqtsnfrvqptesivrfpnitnlcpfdevfnatrfasvyawnrkrisnc	256
S-BA.4-ON907393-USW88525	tlksftvekgiyqtsnfrvqptesivrfpnitnlcpfdevfnatrfasvyawnrkrisnc	356
S-JN.1-WPL05807-OR858200	tlksftvekgiyqtsnfrvqptesivrfpnvtnlcpfhevfnatrfasvyawnrtrisnc	358
3-WPE95661-OR855646	tlksftvekgiyqtsnfrvqptesivrfpnvtnlcpfhevfnatrfasvyawnrtrisnc	354
S-WPE95649-OR855645	tlksftvekgiyqtsnfrvqptesivrfpnvtnlcpfhevfnatrfasvyawnrtrisnc	254
5-WPF60514-OR821989	${\tt tlksftvekgiyqtsnfrvqptesivrfpnvtnlcpfhevfnatrfasvyawnrtrisnc}$	354
S-BA.5-UR063244-ON658807	vadysvlynfapffafkcygvsptklndlcftnvyadsfvirgnevsqiapgqtgniady	416
S-BA.4-ON907292-USW88525	vadysvlynfapffafkcygvsptklndlcftnvyadsfvirgnevsqiapgqtgniady	416
S-JN.1-WPL05807-OR858200	vadysvlynfapffafkcygvsptklndlcftnvyadsfvikgnevsqiapgqtgniady	418
S-WPE95661-OR055646	vadysvlynfapffafkcygvsptklndlcftnvyadsfvikgnevsqiapgqtgniady	414
S-WPE95649-OR855645	vadysvlynfapffafkcygvsptklndlcftnvyadsfvikgnevsqiapgqtgniady	414
S-WPF60514-OR821989	vadysvlynfapffafkcygvsptklndlcftnvyadsfvikgnevsgiapgqtgniady	414
S-BA.5-UR063244-ON658807	nyklpddftgcviawnsnkldskvggnynyryrlfrksnlkpferdisteiyqagnkpcn	476
S-BA.4-ON907292-USW88525	nyklpddftgcviawnsnkldskvggnynyryrlfrksnlkpferdisteiygagnkpcn	476
S-JN.1-WPL05807-OR858200	nyklpddftgcviawnsnkldskhsgnydywyrsfrksklkpferdisteiyqagnkpck	478
3-WPE95661-OR855646	nyklpddftgcviawnsnkldskhsgnydywyrsfrksklkpferdisteiyqagnkpck	474
S-WPE95649-OR855645	nyklpddftgcviawnsnkldskhsgnydywyrsfrksklkpferdisteiyqagnkpck	474
S-WPF60514-OR821989	nyklpddftgcviawnsnkldskhsgnydywyrsfrksklkpferdisteiyqagnkpck	474

Figure 12: Demonstration that even JN.1 has ²⁴LPP and ⁶⁹HV deletions but could not be assigned to as BA.4 or BA.5 subvariant (more than 18 AAs variation in the spike). The part of the alignment was shown. Thus, multi-alignment clearly indicated OR855646, OR855645 and OR821989 were pre-JN.1 or pre-BA.2.86 subvariant (only variation in the ¹⁷MPLF spike insertion).

In figure-13, figure-14 and figure-15, we demonstrated the Swiss-Model structures of JN.1 spike comparing with known 3-D spike structures (7CN8.1.A; 7CJL.1.A; 7CNB.1.A; 8WTJ.1.B). A potential spike trimers 3-D fold was detected as previously reported but basic amino acid protruding wings were also found in the middle (figure-14). The Swiss-Model predicted **Class score** 1.64 for Wuhan spike whereas for JN.1 spike 0.61

suggesting comparable 3D structures well suited for Wuhan spike but in JN.1 spike had much variation which was further clarified by the **MolProbity score** for Wuhan spike 1.54 vs 1.39 for JN.1 spike. The **Ramachandran plot** favored was 94.01% vs 95.08% indicating JN.1 spike protein had more compact 3-D fold than Wuhan spike.



Figure 13: Comparison of SWISS-Model structures of Spike protein from JN.1 (2023) and Wuhan (2019) coronavirus (front view).



JN.1 2023

Figure 14: Longitudinal Swiss-Model view of spike protein of JN.1 omicron coronavirus showing important surface amino acids and postulated wings with basic amino acids. We postulated that mutations and deletions in the JN.1 spike caused more compact well-suited spike tripartite 3-D structure to interact with ACE-2 receptor.





Figure 15: The view of enlarged top point of the tripartite Spike protein amino acids that involved in ACE-2 receptor interactions was shown. We found differences among the interacting amino acids between JN.1 and Wuhan variants. The amino acids from three same subunits were involved in ACE-2 and spike RBD interactions.

We also demonstrated the overwhelming ³⁶⁷⁵SGF deletion in ORF1ab, ³¹ERS deletion in N-protein and 26nt deletion in 3'-UTR respectively in the suppl-Figures (figure-16, figure-17 and figure-18) among the omicron coronaviruses including JN.1 variant. The heterogeneity among the different lineages was evident. Few omicron strains had L452S mutation (L455S in Wuhan) for JN.1 but no ¹⁷MPLF spike insertion was found (accession numbers: OR674602, OR865731 and OR861833). Similarly, Protein ids. WPK95661, WPK95649 and WPF60514 had no ¹⁷MPLF insertion but ²⁴LPP, ⁶⁹HV, ¹⁴⁵Y, ²¹¹N, ⁴⁸³V (NC_045512.2 Wuhan position) deletions and important L452S mutations were detected and could be assigned as pre-JN.1 and pre-BA.2.86 variants.

B-Wuhan-NC_045512-2019	tagtttgtctggttttaagctaaaagactgtgttatgtatg	11340
OY779010-Denmark-4.9.2023	tagtttgaagctaaaagactgtgttatgtatgcatcagctgtagtgttact	11331
0Y854261-20-11-2023-Denmark	tagtttgaagctaaaagactgtgttatgtatgcatcagctgtagtgttact	11331
0Y855842-20-11-2023-Denmark	tagtttgaagctaaaagactgtgttatgtatgcatcagctgtagtgttact	11331
OY855585-20-11-2023-Denmark	tagtttgaagctaaaagactgtgttatgtatgcatcagctgtagtgttact	11331
OR906019-28-11-2023-USA	tagtttgaagctaaaagactgtgttatgtatgcatcagctgtagtgttact	11277
OR882520-8-11-2023-USA	tagtttgaagctaaaagactgtgttatgtatgcatcagctgtagtgttact	11284
OR862048-3-11-2023-USA	tagtttgaagctaaaagactgtgttatgtatgcatcagctgtagtgttact	11229
OR864490-9-11-2023-USA	tagtttgaagctaaaagactgtgttatgtatgcatcagctgtagtgttact	11259
JN.1-OR919554-USA-21-11-2023	tagtttgaagctaaaagactgtgttatgtatgcatcagctgtagtgttact	11281
OR617194-USA-14.9.2023	tagtttgaagctaaaagactgtgttatgtatgcatcagctgtagtgttact	11293
OY790445-Denmark-26.6.2023	tagtttgaagctaaaagactgtgttatgtatgcatcagctgtagtgttact	11331
OY741159-England-19.9.2-2023	tagtttgaagctaaaagactgtgttatgtatgcatcagctgtagtgttact	11331
XBB.1.5.103-OR917012-21-11-2023	tagtttgaagctaaaagactgtgttatgtatgcatcagctgtagtgttact	11196
OR825084-USA-16.10.2023	tagtttgaagctaaaagactgtgttatgtatgcatcagctgtagtgttact	11277
OR886861-USA-19.10.2023	tagtttgaagctaaaagactgtgttatgtatgcatcagctgtagtgttact	11276
JD.1.1-OR916767-USA-17-11-2023	tagtttgaagctaaaagactgtgttatgtatgcatcagctgtagtgttact	11138
FL.1.5.1-OR916447-USA-13-11-2023	tagtttgaagctaaaagactgtgttatgtatgcatcagctgtagtgttact	11187
XBB.1.16.23-OR917017-22-11-2023	tagtttgaagctaaaagactgtgttatgtatgcatcagctgtagtgttact	11259
HV.1-OR817238-USA-26.10.2023	tagtttgaagctaaaagactgtgttatgtatgcatcagctgtagtgttact	11281
EG.5.1.1-OR813264-USA-10-10-2023	tagtttgaagctaaaagactgtgttatgtatgcatcagctgtagtgttact	11281

Figure 16: Genome-wide search and multi-alignment to demonstrate the ³⁶⁷⁵SGF deletion in the nsp6 protein of ORF1ab polyprotein of most omicron corona viruses. Part of the alignment was shown.

Accession no/variant/date	N protein region	Position
MZ821602-B.1.1.7-30.7.2021	e egeattacgtttggtggacceteag atteaactggcagtaaccagaatgg agaacgcag	28322
OM542166-B.1.617.2-22.11.2021	ccgcattacgtttggtggacceteagattcaactggcagtaaccagaatggagaacgcag	28324
NC 045512-CN-0.12.2019	ecgcattacgtttggtggacceteagattcaactggcagtaaccagaatggagaacgcag	28371
BA.1-OM003685-27.11.2021	eegeattacgtttggtggacceteagattcaactggcagtaaccagaatgg	28339
ON907393-BA, 4-14, 6, 2022	egeattacgtttggtggacceteagattcaactggcagtaaccagaatgg	28279
OP647004-BA. 5.2.1-9.7.2022	ecgcattacgtttggtgggccctcagattcaactggcagtaaccagaattt	28236
OP440319-BF. 7-26.8.2022	eggeattacgtttggtggggcceteagatteaaetggeagtaaceagaattt	28313
JN.1-OR919554-21-11-2023	ecgcattacgtttggtggacceteagattcaactggcagtaaccagaatgt	28293
OR603751-FD.1.1-12.9.2023	ecgcattacgtttggtggacceteagattcaactggcagtaaccagaatgg	28239
OR603569-FL1.5-11.9.2023	ecgcattacgtttggtggacceteagattcaactggcagtaaccagaatgg	28291
OR603183-EG. 5.1-8.9.2023	ecgcattacgtttggtggacceteagatteaactggcagtaaceagaatgg	28339
OR603585-HV.1-11.9.2023	ecgcattacgtttggtggacceteagattcaactggcagtaaccagaatgg	28291
OR603226-GK.1.1-9.9.2023	ccgcattacgtttggtggacceteagattcaactggcagtaaccagaatgg	28341
OR603182-XBB.1.16-8.9.2023	ccgcattacgtttggtggacceteagattcaactggcagtaaccagaatgg	28339
OR553334-XBB.1.5.100-28.8.2023	ccgcattacgtttggtggaccetcagattcaactggcagtaaccagaatgg	28287
OR523040-GN.1.1-21.8.2023	ecgcattacgtttggtggaccetcagattcaactggcagtaaccagaatgg	28302

Figure 17: Genome-wide search and multi-alignment to demonstrate the ³¹ERS deletion in the nucleocapsid protein (N gene) in all omicron coronaviruses.

B-Wuhan-NC 045512-2019	tgtgtaacattagggaggacttgaaagagccaccacattttcaccgaggccacgcggagt	29748
OY779010-Denmark-4.9.2023	tgtgtaacattagggaggacttgaaagagecaccacattttcacc	29688
OY854261-20-11-2023-Denmark	tgtgtaacattagggaggaettgaaagageeaceacatttteace	29706
OY855842-20-11-2023-Denmark	tgtgtaacattagggaggacttgaaagagecaccacattttcacc	29706
OY855585-20-11-2023-Denmark	tgtgtaacattagggaggacttgaaagagccaccacattttcacc	29706
OR882520-8-11-2023-USA	tgtgtaacattagggaggacttgaa agagecaccacattttcacc	29656
OR862048-3-11-2023-USA	tgtgtaacattagggaggacttgaaagagecaccacattttcacc	29601
OR864490-9-11-2023-USA	tgtgtaacattagggaggacttgaaagagecaccacattttcacc	29631
JN.1-0R919554-USA-21-11-2023	tgtgtaacattagggaggacttgaa agageeaceacatttteace	29653
OR617194-USA-14.9.2023	tgtgtaacattagggaggacttgaa agagecaccacattttcacc	29650
OY790445-Denmark-26.6.2023	tgtgtaacattagggagtacttgaaagagecaccacattttcacc	29688
OY741159-England-19.9.2-2023	tgtgtaacattagggaggacttgaa agagecaccacattttcacc	29688
XBB.1.5.103-0R917012-21-11-2023	tgtgtaacattagggaggacttgaa agagecaccacattttcacc	29553
OR825084-USA-16.10.2023	tgtgtaacattagggaggacttgaa agagecaccacattttcacc	29634
OR886861-USA-19.10.2023	tgtgtaacattagggaggacttgaa agagecaccacattttcacc	29633
HV.1-OR817238-USA-26.10.2023	tgtgtaacattagggaggacttgaa agageeaceacatttteace	29653
EG.5.1.1-OR813264-USA-10-10-2023	tgtgtaacattagggaggacttgaaagagecaccacattttcacc	29653

B-Wuhan-NC 045512-2019	acquire guid acquire a	29808
OY779010-Denmark-4,9,2023	nnnnnnnnnnnnnnnnnnnnnnnnnnnnnnnnn	29737
0Y854261-20-11-2023-Denmark	tacagtgaacaatgctagggagagetgcctatatggaagagccctaatg	29755
OY855842-20-11-2023-Denmark	tacagtgaacaatgctagggagagetgeetatatggaagageeetaatg	29755
0Y855585-20-11-2023-Denmark	tacagtgaacaatgctagggagagetgeetatatggaagageeetaatg	29755
OR882520-8-11-2023-USA	tacagtgaacaatgctagggagagetgcctatatggaagagceetaatg	29705
OR862048-3-11-2023-USA	tacagtgaacaatgctagggagagetg	29628
OR864490-9-11-2023-USA	3'-UTRtacagtgaacaatgctagggagagetgeetatatggaagageeetaatg	29680
JN.1-0R919554-USA-21-11-2023	tacagtgaacaatgctagggagagetgcctatatggaagagecetaatg	29702
OR617194-USA-14.9.2023	tacagtgaacaatgctagggagagetgeetatatggaagagecetaatg	29699
OY790445-Denmark-26.6.2023	qaqqccacqcqqaqtacqatqaqtqtacaqtqaannnnnnnnnn	29737
OY741159-England-19.9.2-2023	tacagtgaacaatgctagggagagetgeetatatggaagagecetaatg	29737
XBB.1.5.103-0R917012-21-11-2023	tacagtgaacaatgctagggagagetg	29580
OR825084-USA-16.10.2023	tacagtgaacaatgctagggagagctgcctatatggaagagccctaatg	29683
OR886861-USA-19.10.2023	tacagtgaacaatgctagggagagetgcetatatggaagagecetaatg	29682
HV.1-OR817238-USA-26.10.2023	tacagtgaacaatgctagggagagttgcctatatggaagagccctaatg	29702
EG.5.1.1-OR813264-USA-10-10-2023	tacagtgaacaatgctagggagagetgeetatatggaagageeetaatg	29702

Figure 18: Genome-wide search and multi-alignment to demonstrate the 26nt 3'-UTR deletion at nucleotide 29733 position in most recent omicron coronaviruses.

Multi-alignment detected four JN.1 specific new mutations in the ORF1ab polyprotein (figure-19): T170I mutation in the nsp1 and D1600N plus K1973R two mutations in the nsp3 protease whereas R3821K mutation in the nsp6 protein. Similarly, three mutations (D3H, A63T and A104V) in very conserved membrane protein in both BA.2.86 and JN.1 variants were detected whereas A63T mutation was appeared first in BA.2.75 variant (figure-20). Genome wide search predicted that not all JN.1 variants were selected for A104V mutation yet (figure-21). The Swiss Model analysis showed that no gross changes in the 3-D structure of M protein as compared to published SARS-CoV-2 M protein 3-D models (PDB ID: 8CTK.1.A; 7VGGR.1.E; 7Y96.1.A) (figure-22). The News Papers in India are claiming that there are worldwide increase in JN.1 outbreaks. However, sequence data has not deposited yet from India or China or Brazil. Surely, ¹⁷MPLF insertion in spike including important L452S mutation

favored the spread of JN.1 variant. The orf3A trans-activator protein mutation was not found in JN.1 or BA.2.86.1 subvariants whereasT223I mutation was selected in BA.2 and was found in JN.1, BQ.1, BF.1 as well as BA.4 and BA.5 variants. Interestingly orf3A mutation in Alpha variant (T151I), Beta variant (Q57H and S171L), Gamma variant (W131C and S253P) and Delta variant (S26L) were suggested to increase virulence (data not shown). Data submitted by Opentrons P et al (USA) showed a cluster of BA.2.86.1 spread (PP087519) whereas we found many silent mutations (25421 C>T in ORF3a and 26894 C>A in M-protein) in such coronavirus sequences as shown in figure-23. In figure-24, we disclosed the new point mutations in the JN.1 coronaviruses just have selected in one JN.1 subvariant but not in other JN.1 subvariants and ongoing mutations will dictate the future spread. Thus, analysis of such mutations is important task to monitor coronavirus spread in different countries.

ORF1ab-Wuhan-2019	vllrkngnkgagghsygadlksfdlgdelgtdpyedfqenwntkhssgvtrelmrelngg	180
ORF1ab-BA.2.75-ON999338	vllrkngnkgagghrygadlksfdlgdelgtdpyedfqenwntkhssgvtrelmrelngg	180
ORF1ab-BA.2.86-OR857969	vllrkngnkgagghrygadlksfdlgdelgtdpyedfqenwntkhssgvtrelmrelngg	180
ORF1ab-JN.1-OR919554	vllrkngnkgagghrygadlksfdlgdelgtdpyedfqenwntkhssgvirelmrelngg	180
ORF1ab-Wuhan-2019	slrevrtikvfttvdninlhtqvvdmsmtygqqfgptyldgadvtkikphnshegktfyv	1620
ORF1ab-BA.2.75-ON999338	slrevrtikvfttvdninlhtqvvdmsmtygqqfgptyldgadvtkikphnshegktfyv	1620
ORF1ab-BA.2.86-OR857969	slrevrtikvfttvdninlhtqvvdmsmtygqqfgptyldgadvtkikphnshegktfyv	1620
ORF1ab-JN.1-OR919554	slrevrtikvfttvdninlhtqvvdmsmtygqqfgptylngadvtkikphnshegktfyv	1620
ORF1ab-Wuhan-2019	pnasfdnfkfvcdnikfaddlngltgykkpasrelkvtffpdlngdvvaidykhytpsfk	1980
ORF1ab-BA.2.75-ON999338	pnasfdnfkfvcdnikfaddlnqltgykkpasrelkvtffpdlngdvvaidykhytpsfk	1980
ORF1ab-BA.2.86-OR857969	pnasfdnfkfvcdnikfaddlnqltgykkpasrelkvtffpdlngdvvaidykhytpsfk	1980
ORF1ab-JN.1-OR919554	pnasfdnfkfvcdnikfaddlnqltgykkpasrelkvtffpdlngdvvaidyrhytpsfk	1980

ORF1ab-Wuhan-2019	lvycflgyfctcyfglfcllnryfrltlgvydylvstqefrymnsqgllppknsidafkl	3840
ORF1ab-BA.2.75-ON999338	lvycflgyfctcyfglfcllnryfrltlgvydylvstqefrymnsqgllppknsidafkl	3837
ORF1ab-BA.2.86-OR857969	lvycflgyfctcyfglfcllnryfrltlgvydylvstqefr m nsqgllppknsidafkl	3837
ORF1ab-JN.1-OR919554	lvycflgyfctcyfglfcllnryfrltlgvydylvstqe fk mnsqgllppknsidafkl	3837

Figure 19: The JN.1 coronavirus variant specific ORF1ab polyprotein mutations. The mutations T170I, D1600N, K1973R and R3821K were detected (NC_045512/YP_009724389 based position numbering).

M-BA.2.86-OR857969	mahsngtitveelkklleewnlvigflflawicllqfayanrnrflyiikliflwllwpv	60
M-JN.1-OR919554	mahsngtitveelkklleewnlvigflflawicllqfayanrnrflyiikliflwllwpv	60
M-BA.2.75-ON999338	madsngtitveelkklleewnlvigflfltwicllgfayanrnrflyiikliflwllwpv	60
M-Wuhan-2019	madsngtitveelkklleqwnlvigflfltwicllqfayanrnrflyiikliflwllwpv	60
M-BA.2.86-OR857969	tltcfvlaavyrinwitggiaiamaclvglmwlsyfiasfrlfvrtrsmwsfnpetnill	120
M-JN.1-OR919554	tltcfvlaavyrinwitggiaiamaclvglmwlsyfiasfrlfvrtrsmwsfnpetnill	120
M-BA.2.75-ON999338	tltcfvlaavyrinwitggiaiamaclvglmwlsyfiasfrlfartrsmwsfnpetnill	120
M-Wuhan-2019	tlacfvlaavyrinwitggiaiamaclvglmwlsyfiasfrlfartrsmwsfnpetnill	120
M-BA.2.86-OR857969	nvplhgtiltrplleselvigavilrghlriaghhlgrcdikdlpkeitvatsrtlsyyk	180
M-JN.1-OR919554	nvplhgtiltrplleselvigavilrghlriaghhlgrcdikdlpkeitvatsrtlsyyk	180
M-BA.2.75-ON999338	nvplhgtiltrplleselvigavilrghlriaghhlgrcdikdlpkeitvatsrtlsyyk	180
M-Wuhan-2019	nvplhgtiltrplleselvigavilrghlriaghhlgrcdikdlpkeitvatsrtlsyyk	180
M-BA.2.86-OR857969	lgasqrvagdsgfaaysryrignyklntdhssssdniallvq 222	
M-JN.1-OR919554	lgasqrvagdsgfaaysryrignyklntdhssssdniallvq 222	
M-BA.2.75-ON999338	lgasqrvagdsgfaaysryrignyklntdhssssdniallvq 222	
M-Wuhan-2019	lgasqrvagdsgfaaysryrignyklntdhssssdniallvq 222	
	* * * * * * * * * * * * * * * * * * * *	

Figure 20: Important mutations (D3H, A63T, A104V) in the Membrane protein of JN.1 and BA.2.86 variants.

	Acc. no./date/country	M-protein region	Position
	B-Wuhan-NC_045512-2019	teattgettettteagaetgtttgegegtaegegtteeatgtggteatteaateeagaa	ia 26868
5	OY779010-Denmark-4.9.2023	teattgettettteagaetgtttgegegtaegegtteeatgtggteatttaateeagaa	a 26832
	OY854261-20-11-2023-Denmark	teattgettettteagaetgtttgtgegtaegegtteeatgtggteatttaateeagaa	a 26850
	OY855842-20-11-2023-Denmark	teattgettettteagaetgttig tgegtaegegtteeatgtggteatttaateeagaa	ia 26850
	OY855585-20-11-2023-Denmark	teattgettettteagaetgtttgtgegtaegegtteeatgtggteatttaateeagaa	a 26850
	OR906019-28-11-2023-USA	tcattgettettteagactgtttgtgegtaegegtteeatgtggteatttaateeagaa	ia 26793
	OR882520-8-11-2023-USA	teattgettettteagaetgttggggtaegegtteeatgtggteatttaateeagaa	a 26800
	OR862048-3-11-2023-USA	teattgettettteagaetgtttgtggtaegegtteeatgtggteatttaateeagaasteetgetteetteagaetgttggteatttaateeagaasteetgetg	ia 26745
 <>	OR864490-9-11-2023-USA	tcattgettettteagaetgtttgtgggtaegegtteeatgtggteatttaateeagaa	ia 26775
	JN.1-OR919554-USA-21-11-2023	teattgettettteagaetgttgggtaegegtteeatgtggteatttaateeaga	ia 26797
	OR617194-USA-14.9.2023	teattgettettteagaetgttgegegtaegegtteeatgtggteatttaateeaga	a 26794
	OY790445-Denmark-26.6.2023	teattgettettteagaetgtttgegegtaegegtteeatgtggteatttaateeaga	ia 26832
	OY741159-England-19.9.2-2023	teattgettettteagaetgtutgegegtaegegtteeatgtggteatttaateeagaa	ia 26832
	XBB.1.5.103-0R917012-21-11-2023	teattgettettteagaetgtttgegegtaegegtteeatgtggteatttaateeaga	ia 26697
¢	OR825084-USA-16.10.2023	t cattgettettteagaetgtttgggegtaegegtteeatgtggteatttaateeagaa	a 26778
	OR886861-USA-19.10.2023	teattgettettteagaetgtttgegegtaegegtteeatgtggteatttaateeagaa	ia 26777
	JD.1.1-OR916767-USA-17-11-2023	teattgettettteagaetgtttgegegtaegegtteeatgtggteatttaateeagaa	a 26654
	FL.1.5.1-OR916447-USA-13-11-2023	t cattgettettteagaetgtttgegegtaegegtteeatgtggteatttaateeagaa	ia 26703
	XBB.1.16.23-0R917017-22-11-2023	teattgettettteagaetgtttgegegtaegegtteeatgtggteatttaateeagaa	ia 26775
	HV.1-OR817238-USA-26.10.2023	t cattgettettteagaetgtttgegegtaegegtteeatgtggteatttaateeagaa	ia 26797
	EG.5.1.1-OR813264-USA-10-10-2023	teattgettettteagaetgtttgegegtaegegtteeatgtggteatttaateeagaa	ia 26797
		^	
		12 A104V	

Figure 21: Genome wide search for JN.1 M-protein A104V mutation (red box). It appeared few JN.1 sequences have not introduced A104V mutation yet (green arrows). Interestingly, XBB.1.5.103, PD.1.1, XBB.1.16.23, HV.1, FL.1.5.1 and EG.5.1.1 had no such mutation (blue box)



Normal M dimer

Mutated M dimer

Figure 22: Swiss Model Dimeric 3-D structures of normal M protein of COVID-19 (NC_045512.2) as well as mutated M protein found in JN.1 and BA.2.86 subvariants.



Figure 23: Phylogenetic differences among newly BA.2.86.1 subvariant sequences which were very similar to JN.1 subvariant (data deposited on 7th January, 2024). Important mutations were found 26894C>T with no amino acid change in M-protein (Leucine) and ORF3a 25421 C>T mutation also.



Figure 24: Appearance of new mutations in the JN.1 coronavirus sequences implying hundred subvariants of coronaviruses are still originated every day.

We always check the potential penetration of the specific variant in the database and try to understand their spread in different countries. BLASTP search with mutated nsp1-peptide sequence (vll rkn gnk gag ghr yga dlk sfd lgd elg tdp yed fqe nwn tkh ssg vir elm rel ngg-180) yielded 492 JN.1 sequences (9.1.2024) in the NCBI database. But BLAST search with mutant M-peptide (tlt cfv laa vyr inw itg gia iam acl vgl mwl syf ias frl fvr trs mws fnp etn ill-120) yielded only 98 sequences out of 500 sequences searched indicating most sequences were monopartite deposited from Europe (no protein data uploaded) or all JN.1 or B.2.86 M-protein might not be selected A104V mutation (figure-21). To resolve the issue, we BLASTP searched A63T mutant peptide sequence of M-protein (fly iik lif lwl lwp vtl tcf vla avy rin wit ggi aia mac-86) producing over 5000 sequences (above out search limit due to partial sequences of PCR diagnostics and incomplete sequences with errors). To catch the residual portion of A104V mutants in the NCBI monopartite JN.1 sequences, we BLASTN searched with mutant oligo surrounding A104V mutation (5'-tca ttg ctt ctt tca gac tgt ttg tgc gta cgc gtt cca tgt ggt cat tta atc cag aaa-3') producing more than 1000 sequences. However, with spike mutant oligo BLASTN search (22548-tcc taa tgt tac aaa ctt gtg ccc ttt tca tga agt t) produced over 4984 sequences as before. Such analysis might be useful to conclude that monopartite JN.1 related sequences (starting accession number with "AY") were more in the database signalling more and more JN.1 and BA.2.86.1 subvariants spread in the Europe than USA (at least more JN.1 sequences were deposited from Europe). Major JN.1 sequences obtained from European countries like England (OY990490), Denmark (OY984429),

Switzerland (OY991000), Scotland (OY989956) and Ireland (OY989348). Astonishingly, we found a dated 31.1.2023 coronavirus sequence with only ²⁴LPP spike deletion that also had 22555 A>G mutation as above but no ⁶⁹HV deletion nor ¹⁷MPLF spike insertions. Thus, mutation, deletion and insertion among the different coronaviruses selected under pressure and nomenclature of those very similar sequences remains controversial.

4. Discussion

I was studying the coronavirus NCBI portal and its sequence database since 2020 and had published twenty papers in new open-access journals. Sequence homology search showed that nsp2 was an RNA topoisomerase, nsp13 as capping methyl transferase. and nsp16 as 2'-O-Methyl 2251Uridine RImE rRNA methyltransferase. The mutations, deletions and insertions in new coronavirus variants occurred frequently and various names were introduced for such mutants. The omicron subvariants BF.7 and BQ.1 sequences were greatly diminished recently with the spread of omicron XBB.1 lineages. During database search, subvariants HV.1, JN.1 EG.1 and JD.1 have deposited predominantly (December, 2023). In January, 2024, we found clonal expansion of JN.1 worldwide and thus we studied molecular detail of this coronavirus subvariant to find reason of spread.

The JN.1 coronavirus lineage was originated from BA.2.86 which was also known as Pirola variant and first detected in Denmark [38, 39]. The JN.1 subvariant was first reported in

Luxembourg in August and CDC suggested that its L455S (NC_045512.2 position) mutation might be caused the immune evasion properties. Considering the potential changes in BA.2.86, I would prefer the name JN.1 for BA.2.86 and present JN.1 should be then JN.1.1 and surely BA.2 vs BA.2.75 might understandable but BA.2 vs BA.2.86 would not match at all due to more distinct mutations and deletions in the spike.

We disclosed the ¹⁷MPLF four amino acids spike insertion in JN.1 that might be involved in the higher transmission properties because of compensation eight deletions (24LPP, 69HV, 145Y, ²¹¹N and ⁴⁸³V) in the spike. Data indicated the spread of JN.1 variant was maximum (3.5% of coronavirus sequences in the database) in the Denmark and USA during September, 2023. The JN.1 spread in South India has first detected in December, 2023 but scientists have cautioned such subvariant to be the major variant with 20-30% share of all omicron infections worldwide in 2024. Interestingly, JN.1 showed lower affinity for ACE-2 receptor with higher immune evasion as compared to BA.2.86.1 subvariant [38]. In August, 2023, BA.2.86 was found to be variant of concern (VOC) with many new mutations (WHO) and JN.1 was the precedent of BA.2.86 with one amino acid change in spike. We first time documented the insertion and important spike mutations in JN.1 subvariant as compared to BA.2.86 subvariant and others BA.2 subvariant (BA.2.3, BA.2.9, BA.2.48, BA.2.75). The report suggested EG.5.1, FL.1, XBB.1.5, XBB.1.16, XBB.1.9, XBB.1.42, XBB.2.86, XBB.2.3 were the major coronavirus variants spreading in December, 2023 and the BQ.1, BN.1, CH.1 and BQ.1.1 lineages were gradually diminished since January-March, 2023. The JN.1 variant was spreading highly worldwide and the virus did not replicate in Vero E6 cells and poor fusogenic [39]. The spread of 17MPLF insertion (ATG CCG CTG TTT) in JN.1 spike is important (figure-1) which also has found in BA.2.86 and BA.2.86.1 subvariants but not in lower BA.2 lineages like BA.2.12.1, BA.2.48, BA.2.75 and BA.2.75.10 (figure-9). The database penetration was found for JN.1 and BA.2.86 variants (figure-5 and figure-7) over 500 sequences and maximum in September to December. However, spread of XBB.1.5.103 spike ¹⁷⁶EGKEG deletion mutants were found from June-September, 2023 and only ~75 sequences were detected so far (figure-6 and figure-8). Database suggests that JN.1 is rapidly spreading in the Europe as well as USA. The BA.2.86 variant is deadly as it has acquired the important mutations in the spike including ⁶⁹HV spike deletion and the only main difference between JN.1 and BA.2.86 is spike L452S mutation (L455 in Wuhan) (figure-10). It appears that JN1 ¹⁷MPLF spike insertion is also a driving force for higher transmission compensating eight amino acids deletions. The JN.1 is BA.2.86 precedent and it has no similarity to omicron BA.4 and BA.5 lineage coronaviruses (figure-12) but it has unique 69HV spike deletion which has not seen among other BA.2 lineages including BA.2.75 variant [40].

SWISS-Model predicted a more compact spike (figure-14) although the surface amino acids for interaction with ACE-2 receptor were changed (figure-15). The Swiss-Model structure of JN.1 spike predicted a more compact 3-D tripartite structure to interact with ACE-2 receptor [41-44]. Possibly middle wings

with basic amino acid interacted with viral RNA for quick complete inclusion of virus into lungs cells and thus might be involved for rapid spread among the people whose immunity to COVID-19 vaccines was lost considerably. Spike protein of JN.1 has more mutations and deletions and thus will be less protective to COVAXIN and COVISHILD vaccines [45-51]. The JN.1 coronavirus thus, was more refractile to antibody of previously coronavirus-infected (Omicron BA.1/BA.2/BA.4/BA.5) individual [47, 49].

Data indicated that in the RBD of spike, amino acids Glu484, Phe486, Gln474, Lys417, Tyr453 and Asn501 might be involved to interact with the ACE-2 receptor [49-53]. But our data with JN.1 spike model (figure-15) suggested amino acids His442, Pro482, Lys480, Lys478 might be important in this aspect. As compare with Wuhan coronavirus spike, data indicated Arg346, Phe486, Lys444, Gly446, Val445 and tyr449 might be first interacted. Truly, 3-D crystal structure of JN.1 spike must be known to give a more conclusive data on RBD-ACE-2 interaction, transmission and pathogenicity.

The SARS-CoV-2 variants Delta, Kappa and Lambda with the double mutations T478K/L452R, E484Q/L452R, and F490S/L452Q, respectively, in their receptor binding domains (RBDs) of the spike protein were resistant to antibodies against Wuhan coronavirus but such mutations might not be sufficient to reduce the interaction between RBD and ACE-2 receptor [50, 51]. However, S373L (L368), S375P (P370), S377F (F372), K419N (N414), N442K (K437), G448S (S443), S479N (N474), E486A (A481), Q495R (R490), G498S (S493), Q500R (R495), and Y507H (H502) mutations in the RBD spike of omicron viruses changed such interacted amino acids as reflected in our JN.1 spike modelling data [3, 28]. More interestingly, 15 amino acids were changed further in the JN.1 spike making more confusion in our modelling data as compared to previously published data [49].

Data indicated more JN.1 sequences were deposited from the Europe. Does this imply that more JN.1 spread in Europe than USA? However, our finding of conserved M-protein mutations in BA.2.86 and JN.1 subvariants speculated if M-protein 3-D structure played a role for its higher transmission. Molecular dynamics simulations showed a high degree of structural rigidity in a simple lipid bilayer and supported a role for M homodimers in scaffolding viral assembly. Further, M displayed an important electropositive cytosolic surface that might be important for interactions with N, S, and viral RNA [54]. The D3H, A63T, A104V mutations in the M protein should change the charges in its surface. The M protein domains AA 1-19, AAs 20-40, AAs 51-71 and AAs 80-100 and AAs 101-222 were designated as NTD, TMI, TMII, TMIII and CTD respectively. The common interacting residues of the M-protein with S and N proteins were suggested as C-terminal Phe103, Arg107, Met109, Trp110, Arg131, and Glu135 [55-57]. However, at least we found that Ala104 of M-protein had interacting role with Ser186 of N protein changing M-N interaction in JN.1 and BA.2.86 variants [55].

Such studies are important to develop new drugs against COVID-19. The remdesivir, favipiravir, ribavirin and sofosbuvir drugs used to inhibit viral RNA-dependent RNA polymerase (RdRp), as well as drugs presumably acting on IL6 blockers, tocilizumab and doxycycline, acting on viral entry such as arbidol and hydroxychloroquine, protease inhibitors lopinavirritonavir and darunavir, JAK-1/2 inhibitors baricitinib and ruxolitinib are under different stages of clinical trials but remdesivir plus nirmatrelvir as Paxlovid was now used against COVID-19 worldwide [58-60]. The RBD spike-ACE-2 binding blocker (violacein) will be good candidate drug against RNA viruses [61]. The synthetic peptide like P9R (HOOC-NGA ICW GPC PTA FRQ IGN CGR FRV RCC RIR-NH2) and Peptide-3 (HOOC-DKF NHE AED LFY QSS LAS WNY NT-NH2) suggested to inhibit RBD-ACE-2 interactions to stop COVID-19 replication [62]. Recently, TEMP106B protein was suggested as a new receptor of COVID-19 entry into different human cells and TMEM106B-specific monoclonal antibodies blocked SARS-CoV-2 infection [63]. However, spike substitution E484D increased TMEM106B binding, thereby enhancing TMEM106B-mediated COVID-19 entry providing an alternate route of RBD mutation and COVID-19 spread as likely had happened in JN.1 variant. Thus, more and more drugs will be screened to stop omicron coronavirus spread.

5. Conclusion

Time to time, I am elegantly disclosing the nature of mutations, deletions and insertions in the genome of different coronavirus variants favoring higher transmission. My goal is to track genetic changes among coronavirus variants with time. The new JN.1 ¹⁷MPLF spike insertion variant with L452S mutation is spreading highly worldwide. Similarly, XBB.1.5.103 176EGKEG deletion in the spike with popular ORF8 gene GGA=TGA termination codon mutation in XBB.1.103, XBB.1.16.23 as well as highly transmissible HV.1, EG.5.1.1 and FL.1.5.1 is important VIC to consider for further study. Surely, inactivation of nsp1, ORF7a and ORF8 small immuno-regulatory proteins lower the pathogenic potential of coronaviruses and such deletions were not detected in JN.1. It was therefore suggested that predominance of 69HV deletion and RBD mutations in JN.1 might be due to favorable escape of coronaviruses from immune-drugs. The JN.1 RBD-ACE-2 and RBD-TMEM106B binding inhibitors may be important drug to curve recent omicron JN.1 coronavirus spread.

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