Using Phylogenetic trees and substitutions to Capture Relationship of SARS-Cov-2 Variants and SARS-like Genomes

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Main Question: How do variants of SARS-COV-2 (Omicron, Alpha, etc.) and other SARS-like genomes compare to each other?

Background & Significance:
The COVID19 pandemic created a newfound necessity for research in SARS-COV-2 viruses and variants. Since the start of the pandemic more and more variants have been discovered and sequenced. We will use different algorithms to create multiple phylogenetic trees. This will illustrate the different evolutionary relationships between variants and SARS-like genomes. Using multiple algorithms will allow us to create a clear picture of the evolutionary relationship and compare algorithm outputs. Most people do not understand the difference between any of the SARS genomes enough to care about getting an updated shot, so this should help people understand the differences between them to get them thinking about updated covid shots.

Data:
We will use SARS-Cov-2, variants, and SARS-like genomes that can be downloaded from the NCBI website (data files are prepared by Dr. Hou). We will also use the multi-alignment and pairwise alignment data files provided. Each genome has around 30K DNA bases. We will first conduct all vs. all genome comparison and obtain the similarity measurement between every pair of genomes. The similarity is a numeric value between 0 and 1.

The study methods:
A comparison of phylogenetic trees will be used to show differences and similarities between SARS-COV-2, variants, and SARS-like genomes. This will help show why the different genomes and given different names and why SARS-COV-2 variants are variants instead of a different SARS-like genome. We will calculate branch lengths for each algorithm and compare trees. We used distance matrices and BioPython library to get the output on a specific phylogenetic tree. In the case of low substitution rate, we expect the branches to be close together. In the case of high substitution rates, we expect the branches to be far apart from one another. We will first start with the SARS-COV-2 and variants, then move onto SARS-like genomes. Graphs will be constructed and provided as a visual aid to view the data that is found and collected.

Programming language & system: Java, Linux, Python

Library packages: BioJava, Biopython, Matplotlib, ETE

Hours: Liz- 8hours, Kleo- 12hours, Chris-12 hours, Roberto- 8hours

Work environment: GitHub will be used for collaboration on all files and research.

Contribution: Liz – report writing, graph designing, presentation designing 25 %
Kleo - design of the program, implementation/debugging/documentation 25 %
Chris - design of the program, implementation/debugging/documentation 25 %
Roberto - report writing, graph designing, presentation designing 25 %

Initial data (same from proposal):

PW FILE	SCORE	MATCHES	SUBSTITUTIONS	INDELS(GAPS)
SARS2.ALPHA.SING.MAF	2,811,044	29,808	31	10
SARS2.BETA.SING.MAF	2,842,956	29,819	26	18
SARS2.DELTA.SING.MAF	2,839,244	29,761	33	0
SARS2.GAMMA.SING.MAF	2,836,621	29,767	35	13
SARS2.OMICRON.SING.MAF	2,837,255	29,828	39	36
SARS2.SARS.SING.MAF	1,589,514	23,749	5,860	369

Distance matrix based on score

	alpha	beta	delta	gamma	omicron	sars
alpha	0	31,912	28,200	25,577	2,611	1,221,530
beta	31,912	0	3,712	6,335	5,701	1,253,442
delta	28,200	3,712	0	2,623	1,989	1,249,730
gamma	25,577	6,335	2,623	0	634	1,247,107
omicron	26,211	5,701	1,989	634	0	1,247,741
sars	1,221,530	1,253,442	1,249,730	1,247,107	1,247,741	0

Distance matrix based on matches to sars 2

	alpha	beta	delta	gamma	omicron	sars
alpha	0	11	47	41	20	6,059
beta	11	0	58	52	9	6,070
delta	47	58	0	6	67	6,012
gamma	41	52	6	0	61	6,018
omicron	20	9	67	61	0	6,079
sars	6,059	6,070	6,012	6,018	6,079	0

Distance matrix using substitution rate

	alpha	beta	delta	gamma	omicron	sars
alpha	0	1.68×10^{-4}	6.9×10^{-5}	1.36×10^{-4}	2.67×10^{-4}	1.97×10^{-1}
beta	1.68×10^{-4}	0	2.36×10^{-4}	3.03×10^{-4}	4.35×10^{-4}	1.97×10^{-1}
delta	6.9×10^{-5}	2.36×10^{-4}	0	6.7×10^{-5}	1.98×10^{-4}	1.97×10^{-1}
gamma	1.36×10^{-4}	3.03×10^{-4}	6.7×10^{-5}	0	1.31×10^{-4}	1.97×10^{-1}
omicron	2.67×10^{-4}	4.35×10^{-4}	1.98×10^{-4}	1.31×10^{-4}	0	1.97×10^{-1}
sars	1.97×10^{-1}	1.97×10^{-1}	1.97×10^{-1}	1.97×10^{-1}	1.97×10^{-1}	0

Distance matrix using gap rates

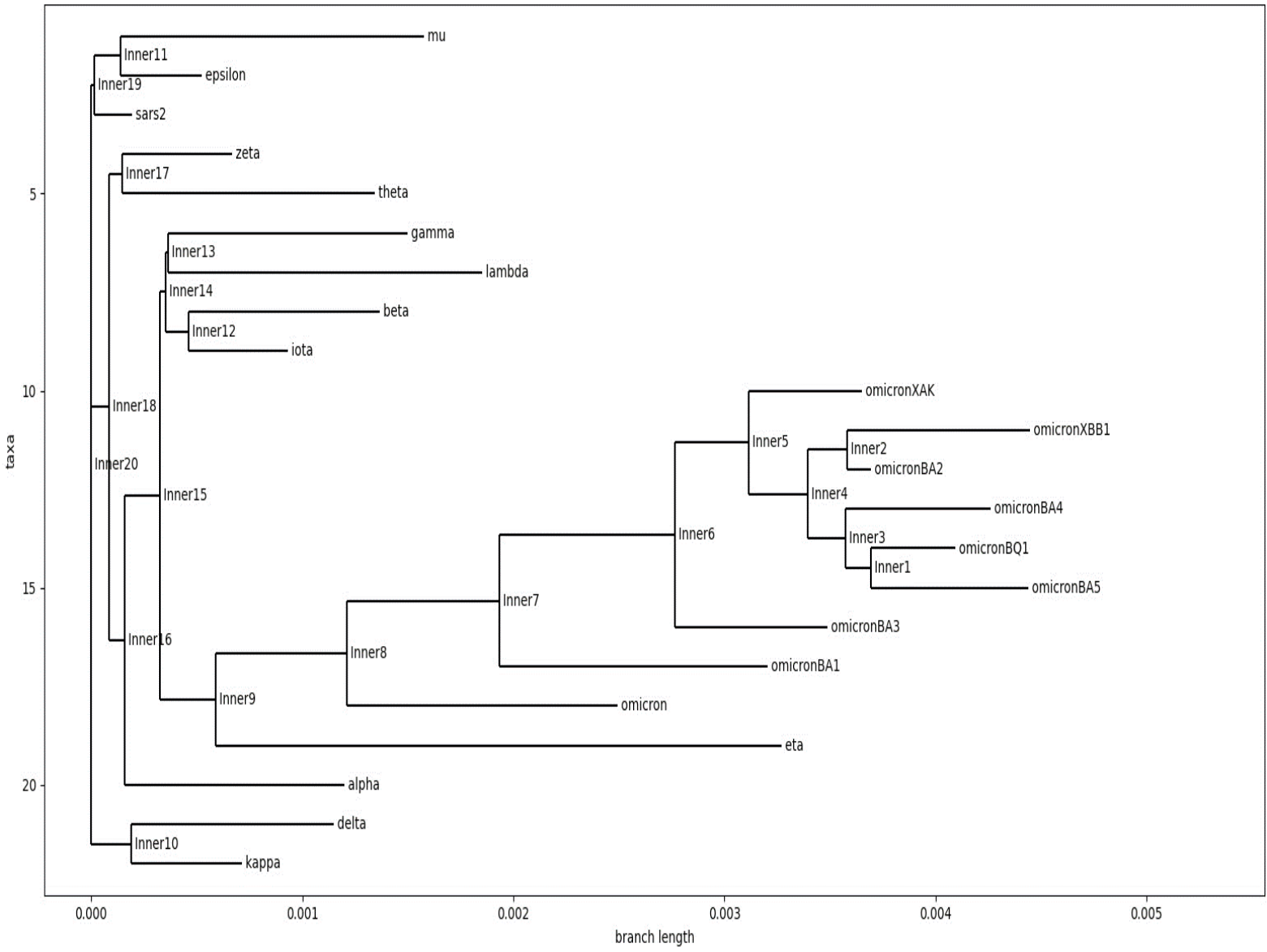
	alpha	beta	delta	gamma	omicron	sars
alpha	0	2.68×10^{-4}	3.35×10^{-4}	1.01×10^{-4}	8.69×10^{-4}	1.20×10^{-2}
beta	2.68×10^{-4}	0	6.03×10^{-4}	1.67×10^{-4}	6.01×10^{-4}	1.17×10^{-2}
delta	3.35×10^{-4}	6.03×10^{-4}	0	4.36×10^{-4}	1.20×10^{-3}	1.23×10^{-2}
gamma	1.01×10^{-4}	1.67×10^{-4}	4.36×10^{-4}	0	7.68×10^{-4}	1.19×10^{-2}
omicron	8.69×10^{-4}	6.01×10^{-4}	1.20×10^{-3}	7.68×10^{-4}	0	1.11×10^{-2}
sars	1.20×10^{-2}	1.17×10^{-2}	1.23×10^{-2}	1.19×10^{-2}	1.11×10^{-2}	0

Distance matrix analysis:
There are 4 different distance matrices above that show how closely related SARS-COV-2 variants and sars are to one another. Comparing the data from all different matrices shows the substantial differences between SARS-COV-2 variants and sars. The variants differences to each other vary within a smaller range of numbers, suggesting some variants are more closely related than others. This is useful in determining precautions to use against each variant.

Substitution rate analysis:
Comparing the wildtype SARS-COV-2 genome to SARS-COV-2 variants and SARS-like genome sars, shows how the substitution rate is substantially greater for sars than any of the variants. Also, the substitution rates comparing sars to variants are within a ~0.002 margin to the substitution rate of sars to SARS-COV-2 of 0.194913. This shows how closely related the variants are compared to one another and the wildtype SARS-COV-2 genome, which is why they are not considered variants of SARS-like genome sars.

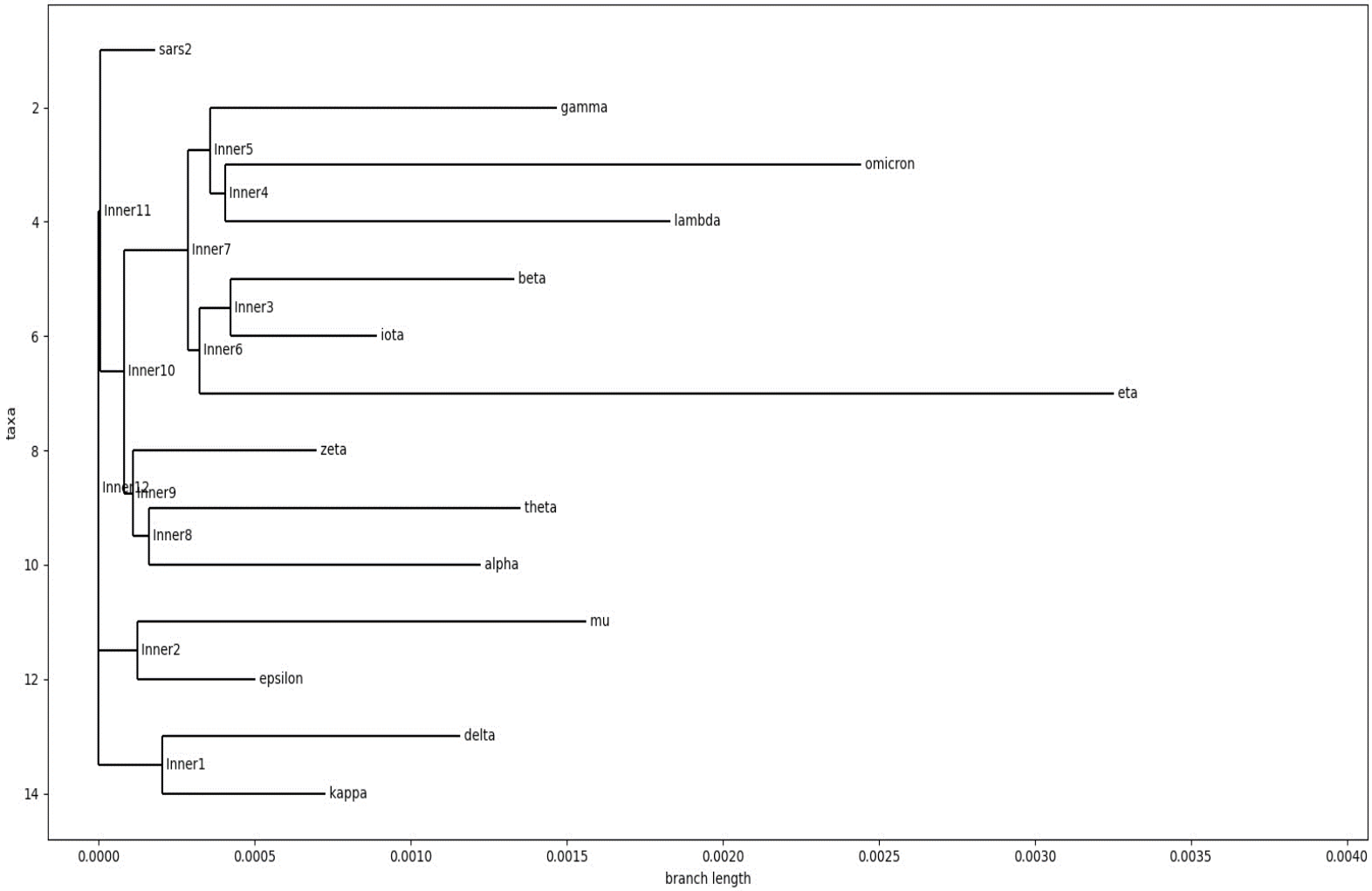
Phylogenetic tree analysis:
As you can see in the tree below, the omicron variants have longer branch lengths and are clustered together. This shows how closely related the omicron variants are, while showing how they differ from other SARS-COV-2 variants. The only SARS-COV-2 variant that has a

relatively similar branch length is eta. Although, more recent omicron variants have longer branches. A branch indicates evolutionary change from the root sars2 and as the branch length increases it shows the amount of evolutionary change also increases. This also suggets how a covid shot that targeted the alpha variant would not be as effective at targeting omicron variants because of how much they changed. More and more variants keep evolving, so it is important to keep an eye on their level of relation to one another to better understand how to take precautionary measures against them.



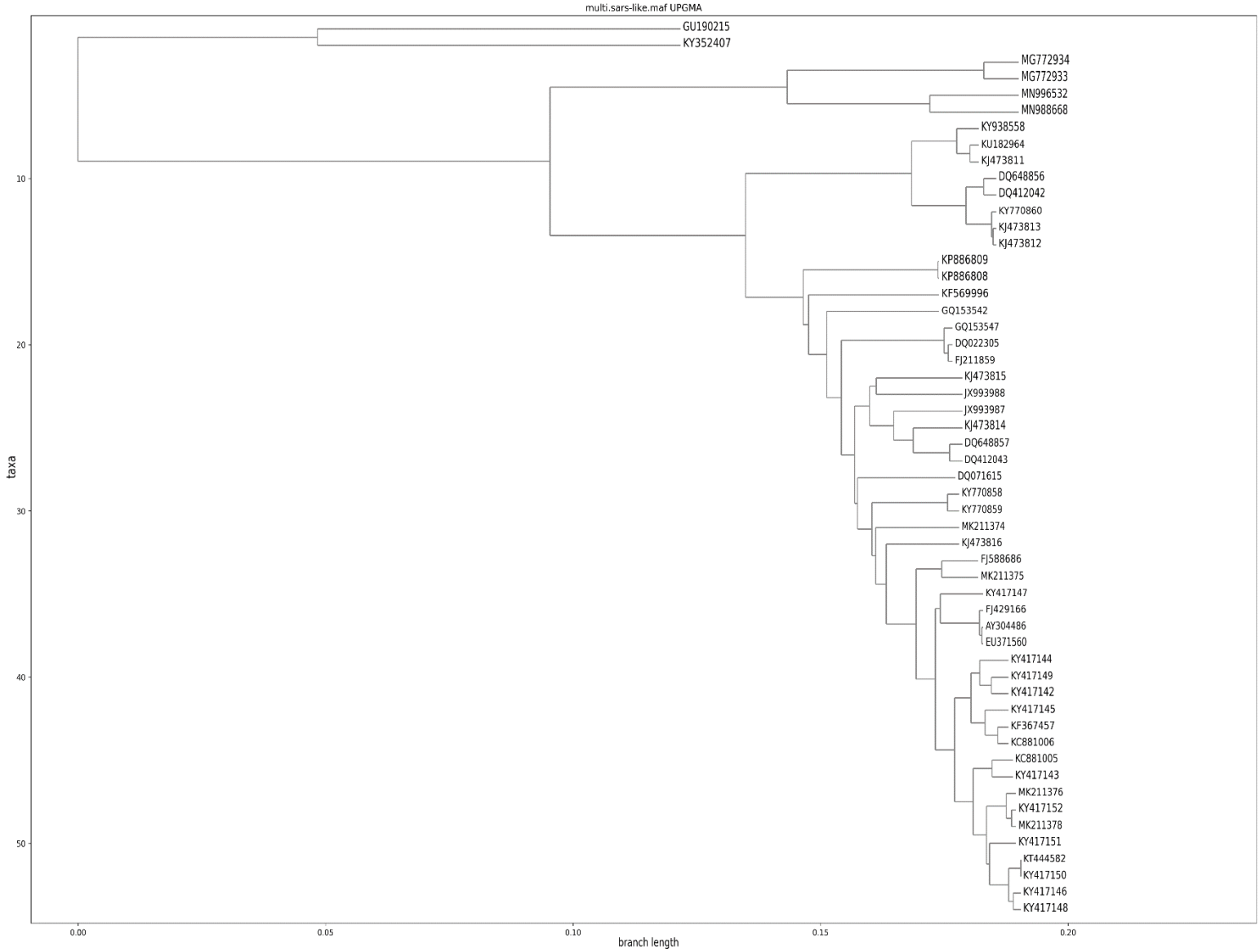
SARS-COV-2 variant tree analysis:
Looking at the tree below that removes omicron variants from the equation can give a better look at how the SARS-COV-2 variants relate to one another. Epsilon shows the least amount of evolutionary change and eta shows the greatest when comparing only SARS-COV-2 variants.

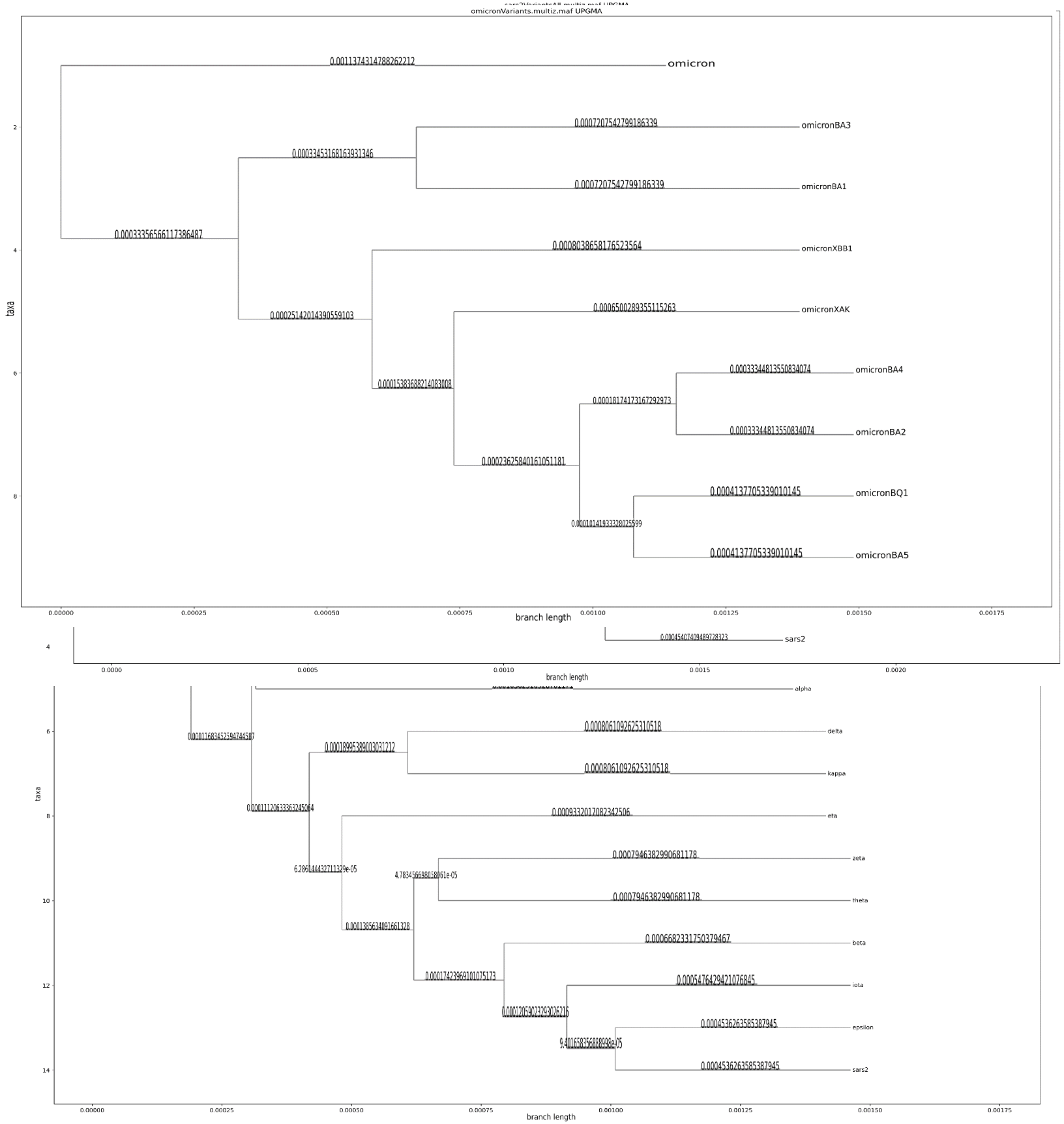
This is determined by considering the branch length. The longer the branch length the more distant an evolutionary relationship.



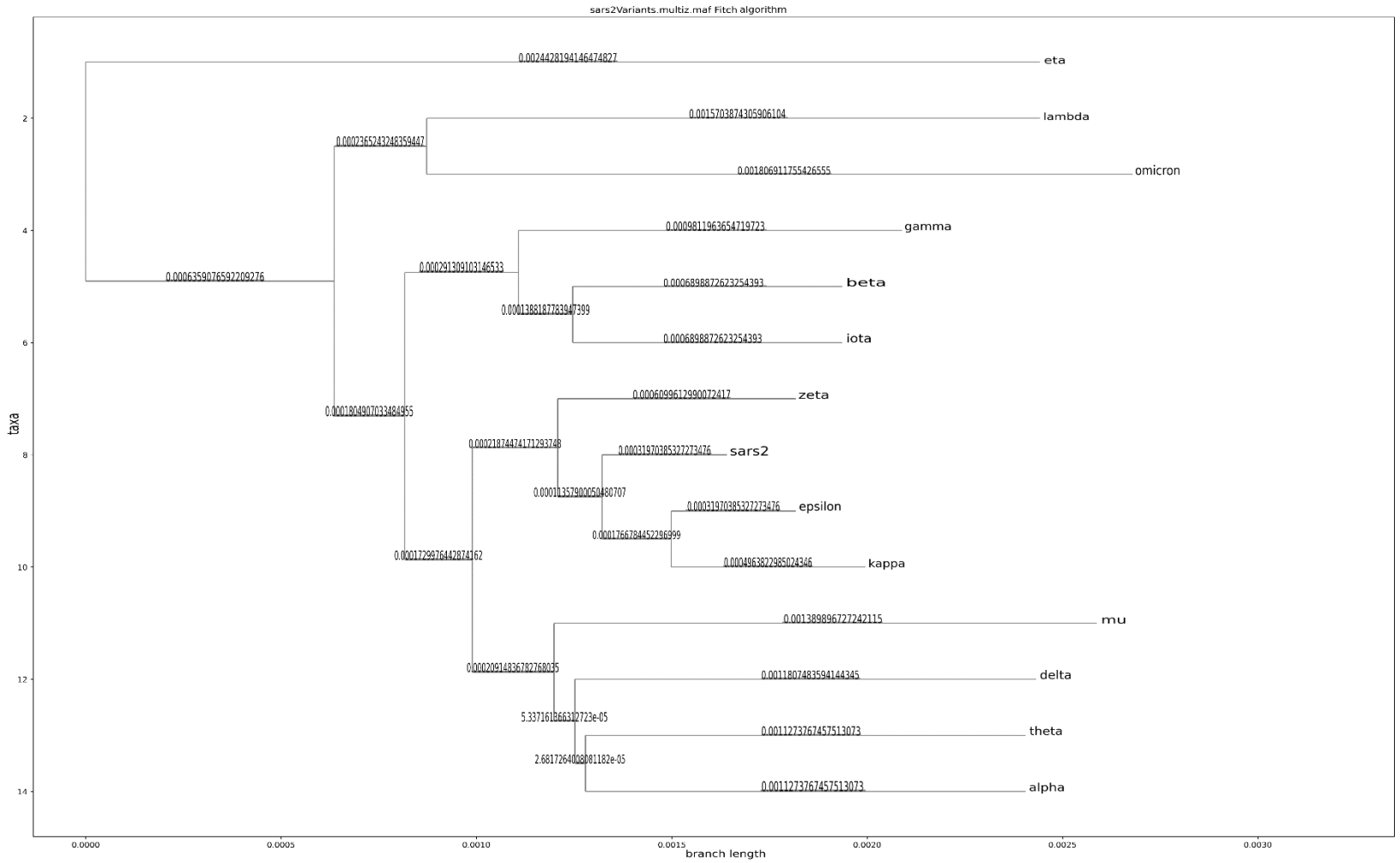
UPGMA Trees analysis:

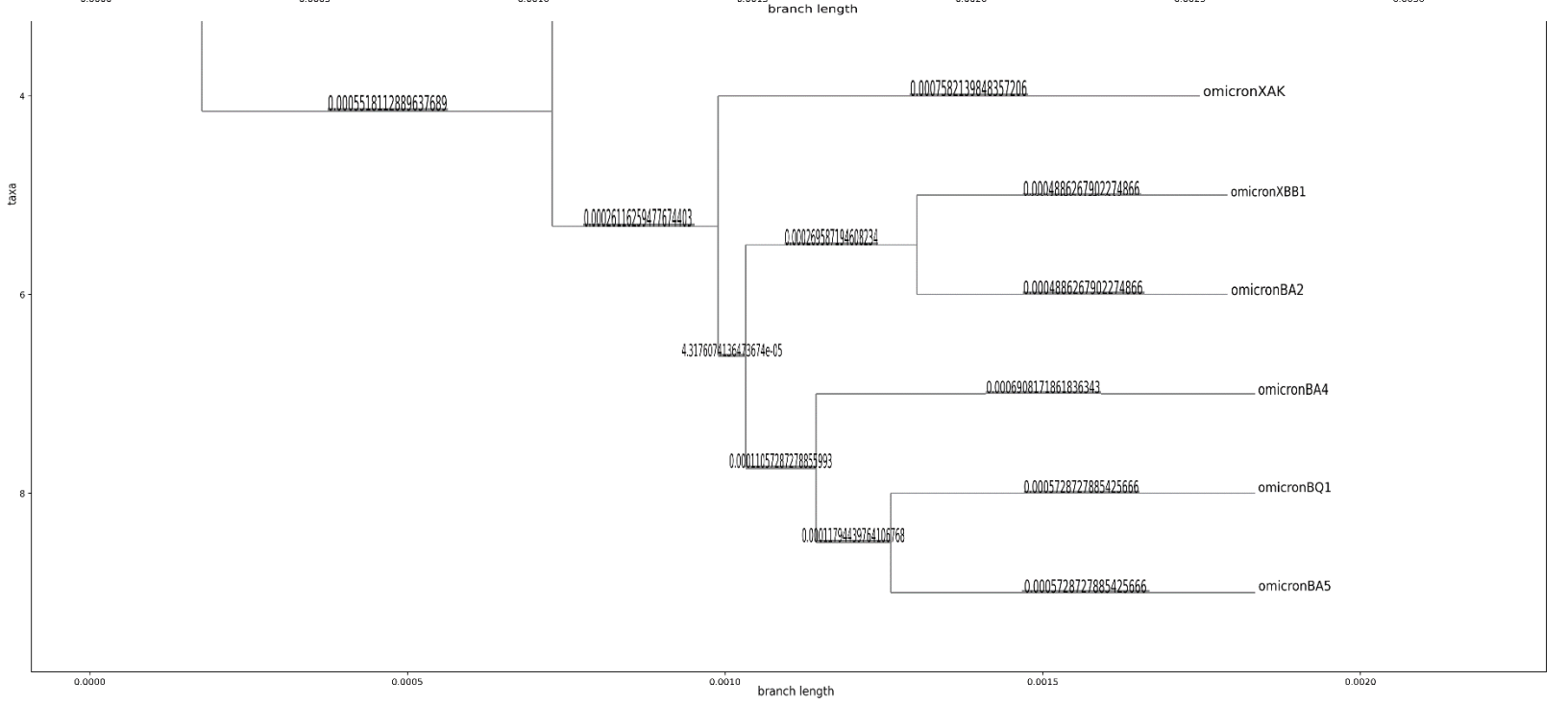
These trees are distance-based trees in which leaves that share the same root have the same distance. The mutation rate is considered a constant throughout the entire tree, which is why the SARS-COV-2 variants branch distances are much more uniform than in the Parsimony branches. UPGMA trees are less reliable than other trees because of the mutation rate considered as constant.




omicronVariants.multiz.maf UPGMA
0.0011374314788262212
omicron
0.0007207542799186339
omicronBA3
0.0003345316816393134 6
0.0007207542799186339
omicronBA1
0.0003335656611738648 7
0.0008038658176523564
omicronXBB1
0.0002514201439055910 3
0.0006500289355115263
omicronXAK
0.0003334481355083407 4
0.0001538368821408300 8
0.0001817417316729297 3
0.0003334481355083407 4
omicronBA2
0.0002362584016105118 1
0.0004137705339010145
omicronBQ1
0.0001014193332802559 9
0.0004137705339010145
omicronBA5
taxa
branch length
0.0004540740948972832 3
sars2
alpha
0.0008061092625310518
delta
0.0001899538900303121 2
0.0008061092625310518
kappa
0.0001116834523947445 87
0.0001112063336324506 4
0.0009332017082342506
eta
6.286144432711329e-05
0.0007946382990681178
zeta
4.783456698058061e-05
0.0007946382990681178
theta
0.0001385634091661328
0.0006682331750379467
beta
0.0001742396910107517 3
0.0005476429421076845
iota
0.0001205902328302621 6
0.0004536263585387945
epsilon
9.401658356888986e-05
0.0004536263585387945
sars2
taxa
branch length

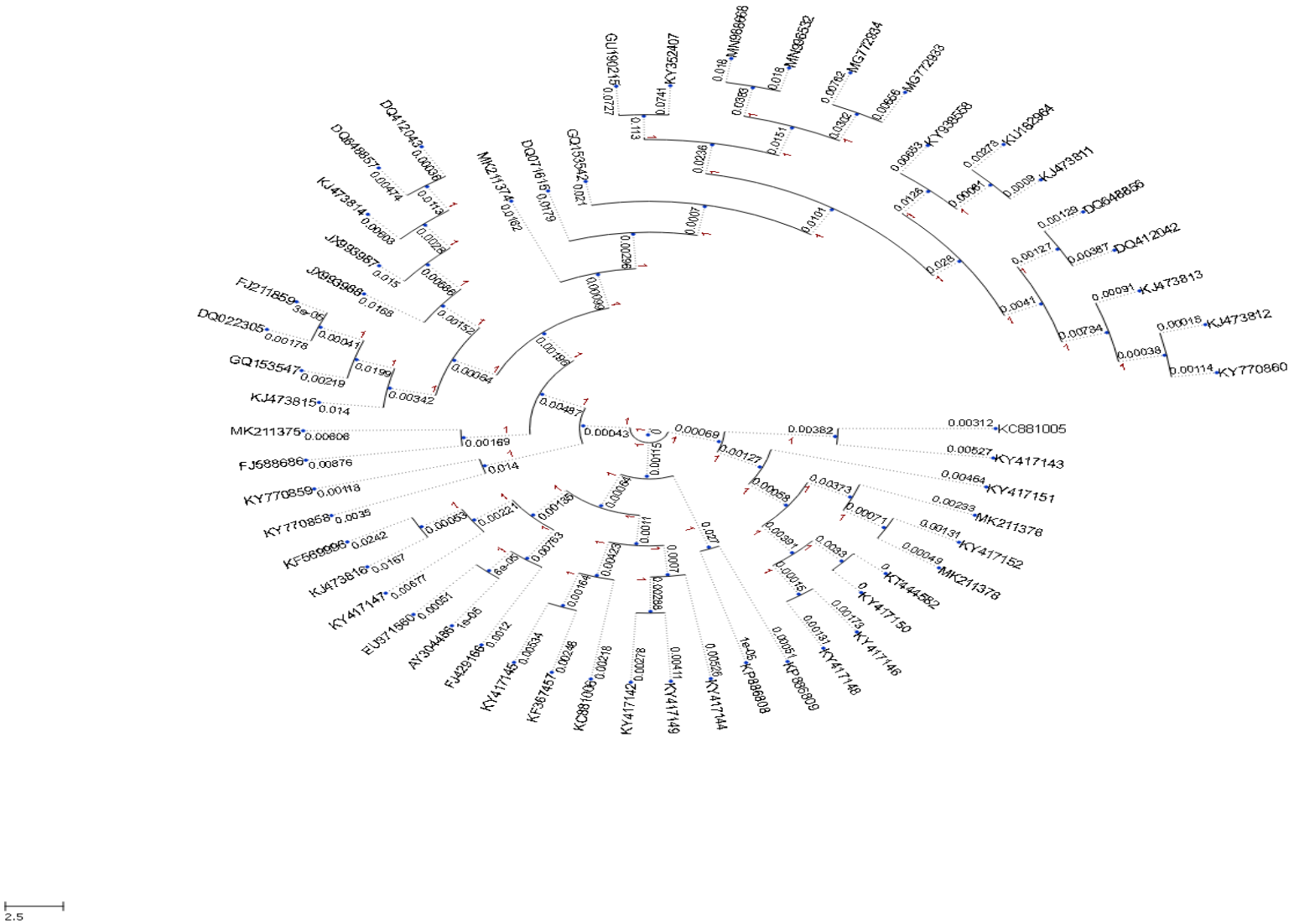
Parsimony trees analysis:
These trees are character-based trees that seek the lowest number of mutations possible for the simplest trees. Parsimony trees on their own give an incomplete picture because of reliance on one method of analysis, but when it is similar to other methods it gives a more complete picture of reliance. These parsimony trees look similar to the UPGMA trees because the algorithm for parsimony uses UPGMA as a base to start. Additionally, the parsimony trees used Fitch's algorthim for simplicity as Sankoff's algorithm is more complicated and takes additional time to complete.


sars2Variants.multiz.maf Fitch algorithm
0.0024428194146474827
eta
0.0015703874305906104
lambda
0.0002365243248359447
0.00180691175542655 5
omicron
0.000981196365471972 3
gamma
0.0006359076592209276
0.0002913091031465 33
0.0006898872623254393
beta
0.0001388187783947399
0.0006898872623254393
iota
0.0006099612990072417
zeta
0.0001804907033484955
0.0002187447417129374 8
0.0003197038532727347 6
sars2
0.0001035790005048070 7
0.0003197038532727347 6
epsilon
0.0001766784452296999
0.0001729976442874162
0.0004963822985024346
kappa
0.0013898967272421 15
mu
0.0002091483678276803 5
0.0011807483594144345
delta
5.337161866312723e-05
0.0011273767457513073
theta
2.681726403081182e-05
0.0011273767457513073
alpha
taxa
branch length
0.0000
0.0005
0.0010
0.0015
0.0020
0.0025
0.0030
2
4
6
8
10
12
14


0.0005518112889637689
0.0007582139848357206
omicronXAK
0.0004886267902274866
omicronXBB1
0.0002611625947767440 3
0.0002695871946082 34
0.0004886267902274866
omicronBA2
4.317607613647 3674e-05
0.0006908171861836343
omicronBA4
0.0001105728727885 5993
0.0005728727885425666
omicronBQ1
0.0001179439764106768
0.0005728727885425666
omicronBA5
taxa
branch length
0.0000
0.0005
0.0010
0.0015
0.0020
4
6
8

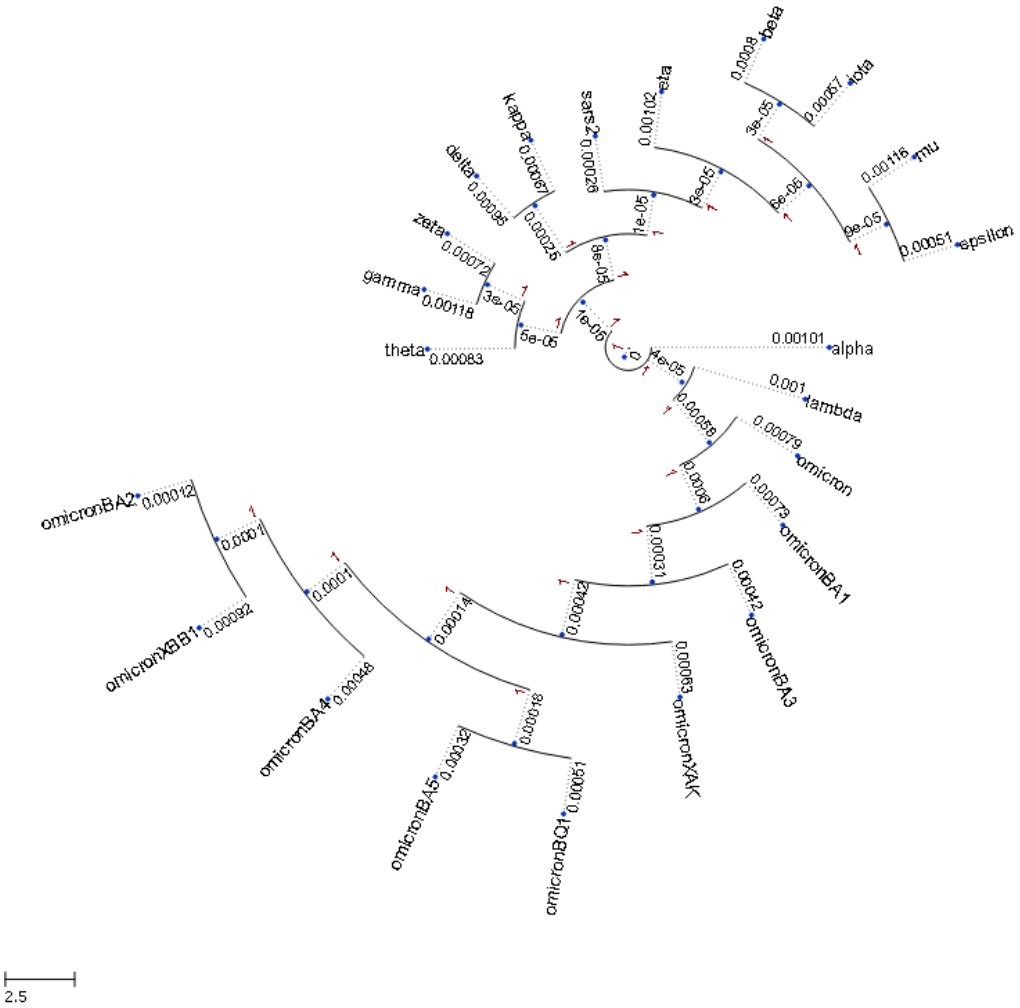
Neighbor-Joining trees analysis:
These trees are distance-based trees that find a pair of leaves close to each other and far from other leaves. This creates an unrooted tree and considers variations on mutation rates, which make it more reliable than trees like UPGMA. As you can see with these trees too the omnicron variants seem to have their own branch and a re more closely related to each other than any other variant.

multi.sars-like.maf Neighbor Joining

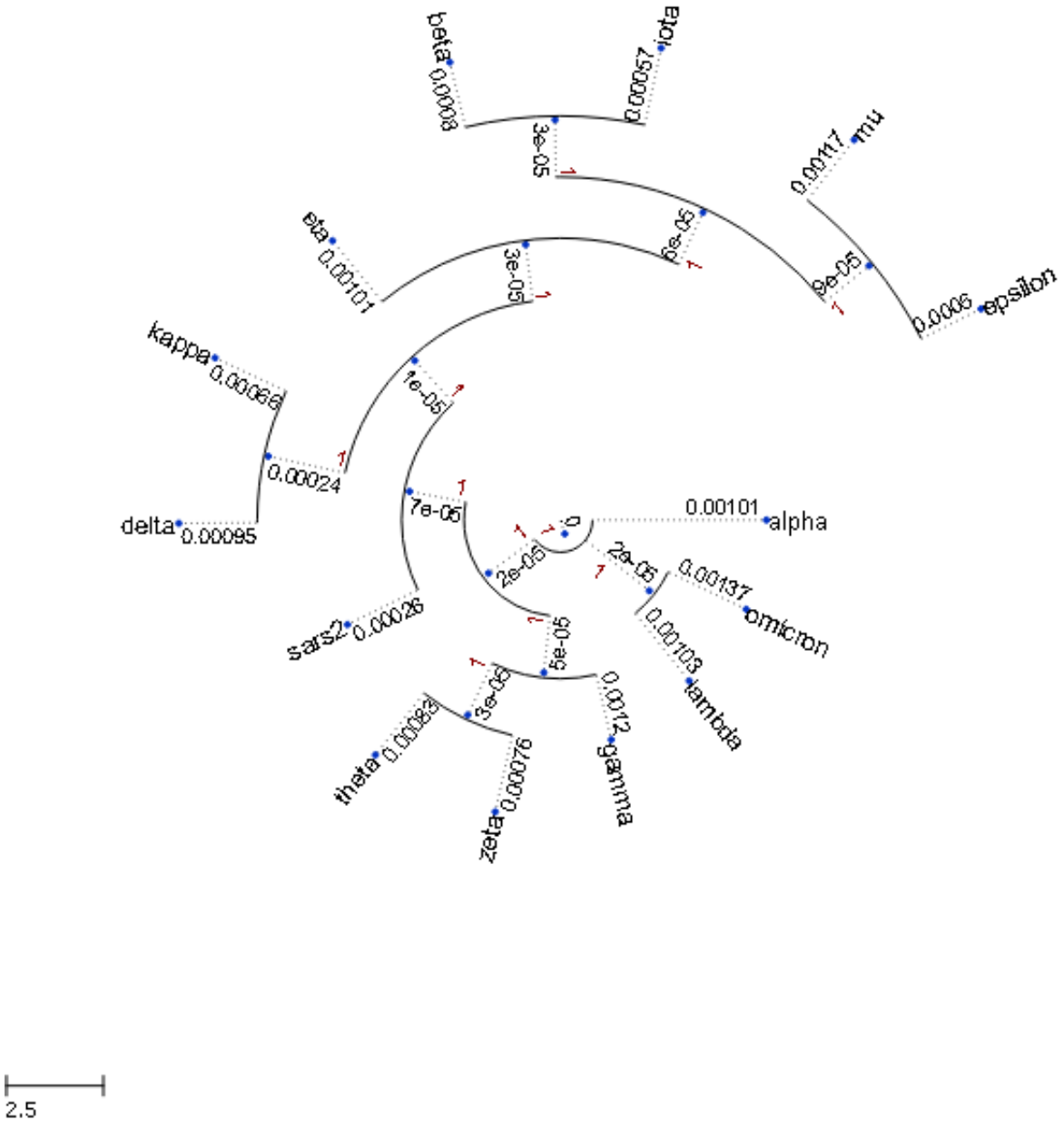


2.5

sars2VariantsAll.multiz.maf Neighbor Joining



sars2Variants.multiz.maf Neighbor Joining



omicronVariants.multiz.maf Neighbor Joining