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# Emerging Monkeypox Virus Sublineage C.1 Causing Community Transmission, Vietnam, 2023

## Appendix

### Genome amplification and sequencing

MPXV whole-genome sequencing was carried out using our established metagenomics based approach that has delivered consistent results for emerging viruses, including MPXV (1–4). In brief, 100  $\mu$ L of sample were pre-treated with 20 U of turbo DNase and 2U RNase I (Ambion-Life Technology, ThermoFisher) at 37°C for 30 min to reduce host genetic background. Nucleic acids (NA) were then isolated from the pre-treated samples using DNeasy Blood & Tissue Kit (QIAGEN), and eluted in 50  $\mu$ L of the elution buffer provided with the extraction kit. Next, the isolated NA was subjected to a pre-amplification step to enrich for viral NA using a non-ribosomal random PCR assay with primers designed to preferentially bind to viral NA but not human ribosomal RNA (1,5). The random PCR procedure was carried out as previously described (1,2). In brief, double-stranded DNA was synthesized from the isolated nucleic acids using a set of 96 non-ribosomal primer (Appendix Table 5), followed by a random amplification step using FR20RV primer (Appendix Table 5). The amplified products were then cleaned up and used as input for whole-genome sequencing. For this step, Illumina COVIDSeq reagents (Illumina) were used to generate DNA library, following manufacturer’s instructions. The concentration and size of the constructed library were accessed using Qubit dsDNA HS kit (Invitrogen) and Agilent High Sensitivity D1000 kit (Aligent Technologies), respectively. Finally, the prepared library was sequenced using MiSeq Reagent kit V3 (150 cycles) or Miseq Nano kit V2 (300 cycles) (Illumina) in a Miseq platform.

## Sequence assembly

A reference-based mapping strategy available in Geneious Prime 2022.2.2 (<https://www.geneious.com>) was applied to generate the consensus from the obtained sequencing reads with consensus calling criteria of  $\geq 5$  reads (6). For this analysis, we use a MPXV sequence (LC760460.1) as a reference. The obtained consensus were further manually edited to clarify the ambiguous positions (if any), and to exclude bases with low quality (i.e., a Phred quality score of  $< 20$ ).

## Assessment of intra-host evolution over the course of illness and PCR confirmatory testing

For investigation of within host evolution over the course of illness, individual positions across the genome were carefully inspected to identify the potential changes leading to non-synonymous substitutions. For this analysis, areas with low sequencing depth (i.e.,  $< 5$  reads with high quality reflected by a Phred quality score of  $\geq 30$ ) were also taken into account during the initial screening step. To rule out potential biases introduced by metagenomic associated steps, potential non-synonymous substitutions were then subjected to confirmatory testing using PCR followed by Sanger sequencing using with primers designed to capture the sequence of interest (Appendix Table 6). Only mutations confirmed by both methods were considered as real substitutions. Synonymous substitutions were not investigated in this study.

## Phylogenetic and mutation analysis

Here we focused our analysis on sublineage C.1. Accordingly, we retrieved all non-redundant whole-genome sequences of this sublineage deposited to GISAID (<https://www.epicov.org/epi3/frontend#3b750a>) or NCBI Virus (taxid: 10244) as of March 28<sup>th</sup> 2024. This resulted in a total of 223 whole-genome sequences of sublineage C.1. For non-C.1 lineages, we used 148 whole-genome sequences representing for geographic regions from which those viruses were isolated as indicated by Nexstrain, including (lineage A (n = 43), sublineage A.1 (n = 20), sublineage A.2 (n = 18), lineage sub A.3 (n = 7), sublineage B.1 (n = 60). Consequently, a total of 385 whole-genome sequence (223 C.1, 148 non-C.1. and 14 from the present study, Appendix Table 7) were included for phylogenetic analysis. A time resolved

phylogenetic tree was then reconstructed using Nextstrain pipeline with Augur v24.2.3. A lineage-A sequence (Accession number: NC\_063383.1) was used to root the tree.

For detection of novel substitutions, we used sequence alignment of sublineage C.1 viruses. We performed the analysis using Nextclade v3.3.1 (<https://clades.nextstrain.org/>), and a lineage-A sequence (Accession number: NC\_063383.1) was used as a reference sequence. Additionally, a global MPXV dataset consisting of 10544 non-redundant sequences retrieved GISAID and the NCBI GenBank (29 July 2024) was assembled to further exclude the presence of such potential novel substitutions in non-C.1 sublineage sequences.

## References

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6. Ladner JT, Beitzel B, Chain PS, Davenport MG, Donaldson EF, Frieman M, et al.; Threat Characterization Consortium. Standards for sequencing viral genomes in the era of high-throughput sequencing. *MBio.* 2014;5:e01360–14. [PubMed](#) <https://doi.org/10.1128/mBio.01360-14>

**Appendix Table 1.** Detailed clinical and laboratory findings of the 3 fatal cases in study of emerging monkeypox virus sublineage C.1 causing community transmission, Vietnam, 2023\*

Characteristic	Patient 04	Patient 13	Patient 17
Age, y	29	27	27
Sex at birth	M	M	M
Duration of hospital stay, d	19	13	29
HIV infection	Yes	Yes	Yes
CD4 cell count, cells/ $\mu$ L	01	16	05
Antiretroviral therapy	No	No	Yes
Mechanical ventilation	Yes	Yes	Yes
Septic shock	Yes	Yes	Yes
Anemia	Yes	Yes	No
Acute respiratory distress syndrome	Yes	Yes	Yes
Acute renal injury	Yes	No	Yes
Acute liver dysfunction	Yes	Yes	Yes
Ocular infection	Yes	Yes	Unknown
No. skin lesions at baseline	>250	101–250	>250
Lesion characteristics			
Necrotizing	Yes	Yes	Yes
Confluent	Yes	Yes	Yes
Size, mm	5–7	20–25	3–7
Comorbidity†	Yes	No	Yes
Tuberculosis	Positive‡	Negative	Not done
Syphilis§	Negative	Positive	Not done
Pneumocystis jirovecii¶	Positive	negative	Not done
Others	<i>Candida albicans</i>	No	<i>Candida spp</i>

\*Patient codes are consistent with those shown in Appendix Figure 1. Virus from P17 was not sequenced.  
†Results of routine culture.  
‡Gastrointestinal and military tuberculosis by Ziehl–Neelsen smear microscopy examination of stool and sputum samples.  
§By rapid test.  
¶By PCR diagnosis.

**Appendix Table 2.** Summary of sequencing results of 14 genome sequences from 14 patients

Sample ID	Sample type	Number of raw reads	Number of mapped reads	Mean sequencing depth (min-max)	% Genome coverage
P01	Lesion swab	2,947,694	1,631,089	1339 (5–17987)	96.07
P02	Lesion swab	3,375,932	2,528,234	963.4 (5–30081)	95.49
P03	Lesion swab	2,018,174	726,272	274.5 (5–9138)	90.29
P04	Lesion swab	3,256,816	2,684,010	1050.7 (5–38317)	96.23
P05	Lesion swab	3,086,716	2,016,767	769.5 (5–26302)	95.27
P06	Lesion swab	3,064,754	309,579	116.8 (5–6485)	72.93
P07	Lesion swab	2,978,534	352,866	132.8 (5–5172)	80.80
P08	Lesion swab	2,778,924	401,856	151 (5–5642)	79.28
P10	Lesion swab	3,787,078	3,453,213	1330 (5–56824)	95.83
P11	Lesion swab	2,199,790	1,338,296	508.1 (5–13463)	89.86
P09	Lesion swab	2,773,716	2,365,381	915.4 (5–43935)	96.46
P14	Lesion swab	877,648	546,075	205.8 (5–7540)	84.46
P13	Lesion swab	3,848,392	3,462,380	1343.1 (5–48465)	98.44
P15	Lesion swab	3,737,842	2,738,850	1053.3 (5–126305)	97.32

**Appendix Table 3.** Frequency, location and associated protein functions of the 12 novel mutations

Novel mutation	Protein Function	APOBEC3-like mutation	Frequency
OPG027:E104K	Host Modulation	Yes	2/14
OPG047:D462Y	Unknown	No	1/14
OPG063:T225S	Transcription	No	1/14
OPG063:N239S	Transcription	No	1/14
OPG068:S428L	Virus Assembly/Budding	Yes	13/14
OPG087:P186T	Transcriptionssss	No	1/14
OPG102:T110A	Transcription	No	1/14
OPG108:N117K	Virulence	No	1/14
OPG118:N76Y	Transcription	No	1/14
OPG138:S170P	Morphogenesis	No	1/14
OPG160:S236P	Morphogenesis	No	1/14
OPG189:I514S	Virulence	No	1/14

**Appendix Table 4.** Results of intra-host evolution investigation of metagenomics reads in samples collected over the course of illness of an advanced HIV patient

Category	Type	Lesion swab (10/2/2023)		Lesion swab(10/9/2023)		Lesion swab (10/16/2023)		BAL (10/19/2023)		Lesion swab (10/11/2023)	
OPG189:I514S	Substitution	Ile to Ser		Ile to Ser		Ile to Ser		Ile to Ser		Ile to Ser	
	Ratio (%)	51	49	22	78	24	76	26	74	22	78
	Sequencing depth	183	176	14	49	29	92	34	96	29	103
OPG187:K233M	Substitution	NA	NA	NA	NA	NA	NA	NA	NA	Lys to Met	
	Ratio (%)	NA	NA	NA	NA	NA	NA	NA	NA	46	54
	Sequencing depth	NA	NA	NA	NA	NA	NA	NA	NA	50	59
OPG060:M147I	Substitution	NA	NA	NA	NA	NA	NA	Ile to Met		NA	NA
	Ratio (%)	NA	NA	NA	NA	NA	NA	0	100	NA	NA
	Sequencing depth	NA	NA	NA	NA	NA	NA	0	4	NA	NA
OPG164:S63C	Substitution	NA	NA	NA	NA	NA	NA	Ser to Cys		NA	NA
	Ratio (%)	NA	NA	NA	NA	NA	NA	0	100	NA	NA
	Sequencing depth	NA	NA	NA	NA	NA	NA	0	2	NA	NA

\*Two nonsynonymous substitutions detected in the BAL collected on 19 October 2023 are in red. Positions carrying single nucleotide polymorphism are indicated by blue. The results of Sanger sequencing of those corresponding positions shown in Appendix Figure 3. NA: indicate positions where no changes were recorded. None of the lesion swabs were collected from the same rash or area.

**Appendix Table 5.** Primer sequences used for non-ribosomal random PCR

Primer	Sequence of primer (5'-3')	Primer	Sequence of primer (5'-3')	Primer	Sequence of primer(5'-3')
FR20RV	GCCGGAGCTCTGCAGATATC	33	GCCGGAGCTCTGCAGATATCTAGTCG	66	GCCGGAGCTCTGCAGATATCTAACGC
1	GCCGGAGCTCTGCAGATATCGATATC	34	GCCGGAGCTCTGCAGATATCGTAGAC	67	GCCGGAGCTCTGCAGATATCGGTAT
2	GCCGGAGCTCTGCAGATATCTAGTAT	35	GCCGGAGCTCTGCAGATATCCTATAG	68	GCCGGAGCTCTGCAGATATCCTCATA
3	GCCGGAGCTCTGCAGATATCTATAGT	36	GCCGGAGCTCTGCAGATATCTAGCTA	69	GCCGGAGCTCTGCAGATATCAATTTG
4	GCCGGAGCTCTGCAGATATCTATATA	37	GCCGGAGCTCTGCAGATATCACTACT	70	GCCGGAGCTCTGCAGATATCCTGGTA
5	GCCGGAGCTCTGCAGATATCATACTA	38	GCCGGAGCTCTGCAGATATCTAACGA	71	GCCGGAGCTCTGCAGATATCTTTCATG
6	GCCGGAGCTCTGCAGATATCATATAT	39	GCCGGAGCTCTGCAGATATCCGACTA	72	GCCGGAGCTCTGCAGATATCGCGATA
7	GCCGGAGCTCTGCAGATATCGTGAC	40	GCCGGAGCTCTGCAGATATCTACTAG	73	GCCGGAGCTCTGCAGATATCACTAAG
8	GCCGGAGCTCTGCAGATATCACTATA	41	GCCGGAGCTCTGCAGATATCAGTAGT	74	GCCGGAGCTCTGCAGATATCGCATA
9	GCCGGAGCTCTGCAGATATCCGTAAT	42	GCCGGAGCTCTGCAGATATCGTTAAC	75	GCCGGAGCTCTGCAGATATCCAATAT
10	GCCGGAGCTCTGCAGATATCCTATAC	43	GCCGGAGCTCTGCAGATATCGTCTAC	76	GCCGGAGCTCTGCAGATATCACCGTA
11	GCCGGAGCTCTGCAGATATCTATACG	44	GCCGGAGCTCTGCAGATATCTACAAG	77	GCCGGAGCTCTGCAGATATCGTGCTA
12	GCCGGAGCTCTGCAGATATCTATGCG	45	GCCGGAGCTCTGCAGATATCTACCAG	78	GCCGGAGCTCTGCAGATATCACGCTA
13	GCCGGAGCTCTGCAGATATCGATACT	46	GCCGGAGCTCTGCAGATATCTGGATT	79	GCCGGAGCTCTGCAGATATCATGTCTG
14	GCCGGAGCTCTGCAGATATCCGTATA	47	GCCGGAGCTCTGCAGATATCTCGTTA	80	GCCGGAGCTCTGCAGATATCAGCTTA
15	GCCGGAGCTCTGCAGATATCGTATAG	48	GCCGGAGCTCTGCAGATATCATAGTA	81	GCCGGAGCTCTGCAGATATCCGACAT
16	GCCGGAGCTCTGCAGATATCCGGTTA	49	GCCGGAGCTCTGCAGATATCATAGTC	82	GCCGGAGCTCTGCAGATATCGCTATA
17	GCCGGAGCTCTGCAGATATCAATAGT	50	GCCGGAGCTCTGCAGATATCCTAGTA	83	GCCGGAGCTCTGCAGATATCGCTATG
18	GCCGGAGCTCTGCAGATATCCGCATA	51	GCCGGAGCTCTGCAGATATCGTACTA	84	GCCGGAGCTCTGCAGATATCTGTAAG
19	GCCGGAGCTCTGCAGATATCATTACG	52	GCCGGAGCTCTGCAGATATCTAAGTT	85	GCCGGAGCTCTGCAGATATCAACTTA
20	GCCGGAGCTCTGCAGATATCTTAACA	53	GCCGGAGCTCTGCAGATATCATATCC	86	GCCGGAGCTCTGCAGATATCATAACG
21	GCCGGAGCTCTGCAGATATCAGTATC	54	GCCGGAGCTCTGCAGATATCTCGATA	87	GCCGGAGCTCTGCAGATATCATGTTA
22	GCCGGAGCTCTGCAGATATCTGTAA	55	GCCGGAGCTCTGCAGATATCGTACCA	88	GCCGGAGCTCTGCAGATATCTGGTAT
23	GCCGGAGCTCTGCAGATATCACTATT	56	GCCGGAGCTCTGCAGATATCGTATCA	89	GCCGGAGCTCTGCAGATATCTGCGTA
24	GCCGGAGCTCTGCAGATATCTAACCG	57	GCCGGAGCTCTGCAGATATCATACTC	90	GCCGGAGCTCTGCAGATATCGGATAT
25	GCCGGAGCTCTGCAGATATCCGATAT	58	GCCGGAGCTCTGCAGATATCACATTA	91	GCCGGAGCTCTGCAGATATCCATAGC
26	GCCGGAGCTCTGCAGATATCGTATAC	59	GCCGGAGCTCTGCAGATATCATATTG	92	GCCGGAGCTCTGCAGATATCCATACT
27	GCCGGAGCTCTGCAGATATCAATCCA	60	GCCGGAGCTCTGCAGATATCCGTCTA	93	GCCGGAGCTCTGCAGATATCCGGATA
28	GCCGGAGCTCTGCAGATATCTAGCAC	61	GCCGGAGCTCTGCAGATATCCTTAGT	94	GCCGGAGCTCTGCAGATATCTTACTA
29	GCCGGAGCTCTGCAGATATCATATCG	62	GCCGGAGCTCTGCAGATATCCTTACA	95	GCCGGAGCTCTGCAGATATCACTCGT
30	GCCGGAGCTCTGCAGATATCAATATT	63	GCCGGAGCTCTGCAGATATCTTATGC	96	GCCGGAGCTCTGCAGATATCTAAGGT
31	GCCGGAGCTCTGCAGATATCTATAGC	64	GCCGGAGCTCTGCAGATATCATACGC		
32	GCCGGAGCTCTGCAGATATCCTTGTA	65	GCCGGAGCTCTGCAGATATCCGCTTA		

**Appendix Table 6.** Primer sequences used for confirmatory experiments

Mutations	Primer direction	Oligo sequences (5'-3')
OPG060:M147I	Forward	GTTAGACAACACACCGACGA
	Reverse	TCAATATCTCCTTCTGGGT
OPG068:S428L	Forward	ACGAGTGCTGCGGACATTAA
	Reverse	ACGAGCCAATTGTCCGTCTA
OPG164:S63C	Forward	ACCGTAGTTGCGGGAACAA
	Reverse	ACCAGCGAAGCTATCATCGT
OPG187:K233M	Forward	TCTAGACGTGGTGATCTAGA
	Reverse	TACTCGACGAAACTCGTCGT
OPG189:I514S	Forward	TGAGATACGGTAGACATCCT
	Reverse	ACGACCATTATCTCCAGCA

**Appendix Table 7.** List of sequences used for phylogenetic analysis

Accession number	Source	Date of collection	Country	Host	Clade	Lineage	Analysis
NC_063383.1	GenBank	2018-08-01	Nigeria	Human	IIb	A	phylogeny
OR500078.1	GenBank	2022-06-29	Romania	Human	IIb	B.1.1	phylogeny
OR500080.1	GenBank	2022-08-16	Romania	Human	IIb	B.1.1	phylogeny
OR500084.1	GenBank	2023-01-05	Romania	Human	IIb	B.1.1	phylogeny
OR500085.1	GenBank	2023-01-26	Romania	Human	IIb	B.1.1	phylogeny
OR464192.1	GenBank	2022-12-01	USA	Human	IIb	B.1	phylogeny
OR459776.1	GenBank	2022-11-15	South Korea	Human	IIb	A.2.1	phylogeny
OR459777.1	GenBank	2022-11-22	South Korea	Human	IIb	A.2.1	phylogeny
OR455100.1	GenBank	2023-08-01	USA	Human	IIb	A.2.1	phylogeny
OR427338.1	GenBank	2023-01-31	USA	Human	IIb	B.1.2	phylogeny
OR427343.1	GenBank	2023-03-01	USA	Human	IIb	B.1.2	phylogeny
OR264418.1	GenBank	2022-07-05	Australia	Human	IIb	B.1	phylogeny
OR264422.1	GenBank	2022-07-13	Australia	Human	IIb	B.1	phylogeny
OR126132.1	GenBank	2023-03-23	Spain	Human	IIb	B.1.4	phylogeny
OR113690.1	GenBank	2023-04-05	Austria	Human	IIb	A.2.2	phylogeny
OR086938.1	GenBank	2022-06-29	Belgium	Human	IIb	B.1	phylogeny
OQ957072.1	GenBank	2023-02-16	Colombia	Human	IIb	B.1.11	phylogeny
OQ773459.1	GenBank	2022-07-01	Germany	Human	IIb	B.1	phylogeny
OQ773518.1	GenBank	2022-07-31	Germany	Human	IIb	B.1	phylogeny
OQ721951.1	GenBank	2023-03-01	Taiwan	Human	IIb	B.1	phylogeny
OQ721953.1	GenBank	2023-03-01	Taiwan	Human	IIb	B.1.3	phylogeny
OQ672572.1	GenBank	2023-01-26	Belgium	Human	IIb	B.1	phylogeny
OQ672573.1	GenBank	2023-01-26	Belgium	Human	IIb	B.1	phylogeny
OQ468900.1	GenBank	2022-07-21	USA	Human	IIb	B.1	phylogeny
OQ451903.1	GenBank	2023-01-23	Germany	Human	IIb	B.1.3	phylogeny
OQ451904.1	GenBank	2023-01-23	Germany	Human	IIb	B.1.3	phylogeny
OQ411312.1	GenBank	2022-06-08	Switzerland	Human	IIb	B.1	phylogeny
OQ261710.1	GenBank	2022-10-21	Colombia	Human	IIb	B.1.10	phylogeny
OP535312.1	GenBank	2018-02-01	Nigeria	Human	IIb	A	phylogeny
OP535313.1	GenBank	2018-01-31	Nigeria	Human	IIb	A	phylogeny
OP535314.1	GenBank	2018-01-31	Nigeria	Human	IIb	A	phylogeny
OP535315.1	GenBank	2018-02-28	Nigeria	Human	IIb	A	phylogeny
OP535316.1	GenBank	2018-02-01	Nigeria	Human	IIb	A	phylogeny
OP535317.1	GenBank	2018-01-31	Nigeria	Human	IIb	A	phylogeny
OP535318.1	GenBank	2017-12-31	Nigeria	Human	IIb	A	phylogeny
OP535319.1	GenBank	2017-12-31	Nigeria	Human	IIb	A	phylogeny
OP535320.1	GenBank	2017-11-01	Nigeria	Human	IIb	A	phylogeny
OP535321.1	GenBank	2017-10-31	Nigeria	Human	IIb	A	phylogeny
OP535322.1	GenBank	2017-10-31	Nigeria	Human	IIb	A	phylogeny
OP535323.1	GenBank	2017-10-01	Nigeria	Human	IIb	A.3	phylogeny
OP535324.1	GenBank	2018-02-01	Nigeria	Human	IIb	A	phylogeny
OP535325.1	GenBank	2018-06-01	Nigeria	Human	IIb	A	phylogeny
OP535326.1	GenBank	2018-06-01	Nigeria	Human	IIb	A	phylogeny
OP535327.1	GenBank	2018-03-02	Nigeria	Human	IIb	A	phylogeny
OP535328.1	GenBank	2018-03-01	Nigeria	Human	IIb	A	phylogeny
OP535329.1	GenBank	2018-03-01	Nigeria	Human	IIb	A	phylogeny
OP535330.1	GenBank	2018-02-01	Nigeria	Human	IIb	A	phylogeny
OP535331.1	GenBank	2018-01-01	Nigeria	Human	IIb	A	phylogeny
OP535332.1	GenBank	2018-01-01	Nigeria	Human	IIb	A	phylogeny
OP535333.1	GenBank	2018-01-31	Nigeria	Human	IIb	A	phylogeny
OP535334.1	GenBank	2018-02-01	Nigeria	Human	IIb	A	phylogeny
OP535335.1	GenBank	2017-10-01	Nigeria	Human	IIb	A.3	phylogeny

Accession number	Source	Date of collection	Country	Host	Clade	Lineage	Analysis
OP535336.1	GenBank	2017-10-01	Nigeria	Human	IIb	A	phylogeny
OP535337.1	GenBank	2017-10-31	Nigeria	Human	IIb	A	phylogeny
OP535338.1	GenBank	2017-10-31	Nigeria	Human	IIb	A	phylogeny
OP535339.1	GenBank	2017-10-01	Nigeria	Human	IIb	A	phylogeny
OP535340.1	GenBank	2017-10-31	Nigeria	Human	IIb	A	phylogeny
OP535341.1	GenBank	2017-10-01	Nigeria	Human	IIb	A	phylogeny
OP959058.1	GenBank	2022-10-27	Colombia	Human	IIb	B.1.2	phylogeny
OP936000.1	GenBank	2022-09-26	Vietnam	Human	IIb	A.2.1	phylogeny
OP936001.1	GenBank	2022-10-19	Vietnam	Human	IIb	A.2.1	phylogeny
OP838893.1	GenBank	2022-06-21	Italy	Human	IIb	B.1.19	phylogeny
OP605560.1	GenBank	2022-07-31	Slovenia	Human	IIb	B.1	phylogeny
OP605572.1	GenBank	2022-07-01	Slovenia	Human	IIb	A.2.1	phylogeny
OP612674.1	GenBank	2019-01-12	Nigeria	Human	IIb	A.1	phylogeny
OP612675.1	GenBank	2019-01-30	Nigeria	Human	IIb	A	phylogeny
OP612677.1	GenBank	2019-03-12	Nigeria	Human	IIb	A.3	phylogeny
OP612678.1	GenBank	2019-03-14	Nigeria	Human	IIb	A	phylogeny
OP612679.1	GenBank	2019-03-14	Nigeria	Human	IIb	A.1	phylogeny
OP612680.1	GenBank	2019-04-01	Nigeria	Human	IIb	A	phylogeny
OP612681.1	GenBank	2019-04-20	Nigeria	Human	IIb	A.1	phylogeny
OP612682.1	GenBank	2019-04-20	Nigeria	Human	IIb	A.1	phylogeny
OP612683.1	GenBank	2019-04-18	Nigeria	Human	IIb	A.1	phylogeny
OP612684.1	GenBank	2019-05-01	Nigeria	Human	IIb	A	phylogeny
OP612685.1	GenBank	2019-05-29	Nigeria	Human	IIb	A.1	phylogeny
OP612686.1	GenBank	2019-06-26	Nigeria	Human	IIb	A.1	phylogeny
OP612687.1	GenBank	2019-07-11	Nigeria	Human	IIb	A.1	phylogeny
OP612688.1	GenBank	2019-11-02	Nigeria	Human	IIb	A.1	phylogeny
OP612689.1	GenBank	2019-12-17	Nigeria	Human	IIb	A.2	phylogeny
OP612690.1	GenBank	2019-12-17	Nigeria	Human	IIb	A.2	phylogeny
OP612691.1	GenBank	2020-01-31	Nigeria	Human	IIb	A.2	phylogeny
OP597769.1	GenBank	2022-09-26	Egypt	Human	IIb	A.2.1	phylogeny
OX344884.1	GenBank	2022-05-24	Spain	Human	IIb	B.1	phylogeny
OX344887.1	GenBank	2022-04-27	Spain	Human	IIb	B.1	phylogeny
OP555485.1	GenBank	2022-07-12	Portugal	Human	IIb	B.1.9	phylogeny
OP555515.1	GenBank	2022-08-01	Portugal	Human	IIb	A.2.3	phylogeny
OP555657.1	GenBank	2022-08-24	Portugal	Human	IIb	B.1	phylogeny
OP536812.1	GenBank	2022-09-01	United Kingdom	Human	IIb	A.3	phylogeny
OP450997.1	GenBank	2022-07-01	USA	Human	IIb	A.2.2	phylogeny
OX336038.1	GenBank	2022-08-31	Slovakia	Human	IIb	B.1	phylogeny
OP422340.1	GenBank	2022-07-13	Austria	Human	IIb	B.1	phylogeny
OP413718.1	GenBank	2022-08-31	United Kingdom	Human	IIb	A.3	phylogeny
OP415232.1	GenBank	2022-08-01	United Kingdom	Human	IIb	B.1.2	phylogeny
OP415283.1	GenBank	2022-08-04	United Kingdom	Human	IIb	B.1	phylogeny
OP382485.1	GenBank	2022-07-05	France	Human	IIb	B.1.12	phylogeny
OP382492.1	GenBank	2022-07-22	France	Human	IIb	B.1.14	phylogeny
OP331335.1	GenBank	2022-06-03	United Kingdom	Human	IIb	A.2.1	phylogeny
OP331336.1	GenBank	2022-06-29	United Kingdom	Human	IIb	A.2.2	phylogeny
OP320548.1	GenBank	2022-07-01	Peru	Human	IIb	B.1.6	phylogeny
OP320554.1	GenBank	2022-07-09	Peru	Human	IIb	B.1.6	phylogeny
OX291694.1	GenBank	2022-08-01	Slovakia	Human	IIb	B.1	phylogeny
OP204857.1	GenBank	2022-08-01	South Korea	Human	IIb	B.1.1	phylogeny
OP160532.1	GenBank	2022-06-01	Netherlands	Human	IIb	B.1	phylogeny
OP144215.2	GenBank	2022-05-30	Belgium	Human	IIb	B.1	phylogeny
OP133007.1	GenBank	2022-07-22	Austria	Human	IIb	B.1	phylogeny
ON918611.1	GenBank	2022-06-20	South Africa	Human	IIb	B.1.7	phylogeny
ON927248.1	GenBank	2022-06-24	South Africa	Human	IIb	B.1.7	phylogeny
ON983168.1	GenBank	2022-04-28	Czech Republic	Human	IIb	B.1.3	phylogeny
ON959143.1	GenBank	2022-06-16	Finland	Human	IIb	B.1.10	phylogeny
OL504741.1	GenBank	2019-12-15	United Kingdom	Human	IIb	A.1	phylogeny
OL504742.1	GenBank	2019-12-15	United Kingdom	Human	IIb	A.1	phylogeny



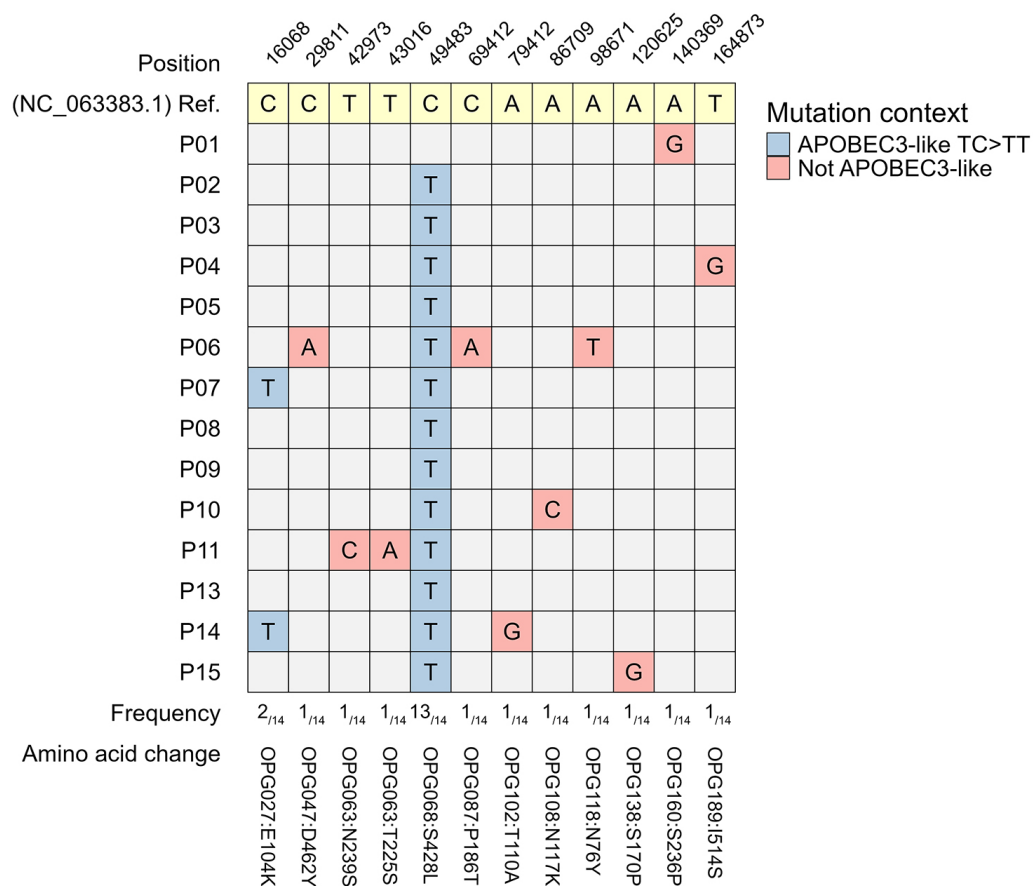
Accession number	Source	Date of collection	Country	Host	Clade	Lineage	Analysis
OL504743.1	GenBank	2019–12–16	United Kingdom	Human	IIb	A.1	phylogeny
ON918656.1	GenBank	2022–06–30	Taiwan	Human	IIb	B.1.5	phylogeny
ON911481.2	GenBank	2022–06–28	Mexico	Human	IIb	B.1	phylogeny
ON880413.1	GenBank	2022–06–14	Brazil	Human	IIb	B.1.12	phylogeny
ON880530.1	GenBank	2022–05–29	Canada	Human	IIb	B.1	phylogeny
ON880531.1	GenBank	2022–05–29	Canada	Human	IIb	B.1	phylogeny
ON872184.1	GenBank	2022–05–30	Ireland	Human	IIb	B.1	phylogeny
ON782022.1	GenBank	2022–05–31	Finland	Human	IIb	B.1	phylogeny
ON745215.1	GenBank	2022–05–19	Italy	Human	IIb	B.1	phylogeny
ON751962.1	GenBank	2022–06–07	Brazil	Human	IIb	B.1	phylogeny
ON674051.1	GenBank	2022–05–01	USA	Human	IIb	A.2.1	phylogeny
ON675438.1	GenBank	2022–05–01	USA	Human	IIb	A.2	phylogeny
ON676707.1	GenBank	2021–07–31	USA	Human	IIb	A.2.3	phylogeny
ON676708.1	GenBank	2021–11–01	USA	Human	IIb	A.1.1	phylogeny
ON649879.1	GenBank	2022–05–20	Israel	Human	IIb	B.1	phylogeny
OX009124.1	GenBank	2022–05–22	Sweden	Human	IIb	B.1.14	phylogeny
ON622720.2	GenBank	2022–05–24	Switzerland	Human	IIb	B.1	phylogeny
ON615424.1	GenBank	2022–05–31	Netherlands	Human	IIb	B.1	phylogeny
MT903337.1	GenBank	2018–01–01	Nigeria	Human	IIb	A	phylogeny
MT903338.1	GenBank	2018–01–01	Nigeria	Human	IIb	A	phylogeny
MT903339.1	GenBank	2018–01–01	Nigeria	Human	IIb	A	phylogeny
MT903341.1	GenBank	2018–08–14	Nigeria	Human	IIb	A.1	phylogeny
MT903342.1	GenBank	2019–05–30	Singapore	Human	IIb	A.1	phylogeny
MT903343.1	GenBank	2018–09–30	United Kingdom	Human	IIb	A.1	phylogeny
MT903344.1	GenBank	2018–09–22	United Kingdom	Human	IIb	A.1	phylogeny
MT903345.1	GenBank	2018–09–22	United Kingdom	Human	IIb	A.1	phylogeny
MT250197.1	GenBank	2019–06–07	Singapore	Human	IIb	A.1	phylogeny
MN648051.1	GenBank	2018–10–04	Israel	Human	IIb	A.1	phylogeny
MK783027.1	GenBank	2017–11–09	Nigeria	Human	IIb	A	phylogeny
MK783028.1	GenBank	2017–11–09	Nigeria	Human	IIb	A	phylogeny
MK783029.1	GenBank	2017–12–06	Nigeria	Human	IIb	A	phylogeny
MK783030.1	GenBank	2017–11–30	Nigeria	Human	IIb	A	phylogeny
MK783031.1	GenBank	2017–11–09	Nigeria	Human	IIb	A	phylogeny
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MK783033.1	GenBank	2017–10–09	Nigeria	Human	IIb	A.3	phylogeny
MG693723.1	GenBank	2017–12–31	Nigeria	Human	IIb	A.3	phylogeny
MG693724.1	GenBank	2017–12–31	Nigeria	Human	IIb	A	phylogeny
EPI_ISL_19108154	GISAID	2023–10–02	Vietnam	Human	IIb	C.1	phylogeny&intra-host mutation
EPI_ISL_19108159	GISAID	2023–10–02	Vietnam	Human	IIb	C.1	phylogeny
EPI_ISL_19108160	GISAID	2023–10–02	Vietnam	Human	IIb	C.1	phylogeny
EPI_ISL_19108161	GISAID	2023–10–04	Vietnam	Human	IIb	C.1	phylogeny
EPI_ISL_19108162	GISAID	2023–10–05	Vietnam	Human	IIb	C.1	phylogeny
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EPI_ISL_18993959	GISAID	2024–01–15	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_18993966	GISAID	2024–01–13	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_18993967	GISAID	2023–12–21	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_18993961	GISAID	2023–12–27	Portugal	Human	IIb	C.1	phylogeny
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EPI_ISL_18702237	GISAID	2023–10–13	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_18702236	GISAID	2023–09–22	Portugal	Human	IIb	C.1	phylogeny
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EPI_ISL_18702243	GISAID	2023–10–27	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_18228634	GISAID	2023–08–02	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_18553811	GISAID	2023–09–19	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_18553850	GISAID	2023–08–21	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_18228630	GISAID	2023–08–01	Portugal	Human	IIb	C.1	phylogeny

Accession number	Source	Date of collection	Country	Host	Clade	Lineage	Analysis
EPI_ISL_18659829	GISAID	2023-10-15	Netherlands	Human	IIb	C.1	phylogeny
EPI_ISL_18971017	GISAID	2023-11-08	Brazil	Human	IIb	C.1	phylogeny
EPI_ISL_18659828	GISAID	2023-08-29	Netherlands	Human	IIb	C.1	phylogeny
EPI_ISL_18746884	GISAID	2023-12-18	Netherlands	Human	IIb	C.1	phylogeny
EPI_ISL_18553829	GISAID	2023-08-07	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_18228645	GISAID	2023-07-21	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_18689511	GISAID	2023-11-22	Germany	Human	IIb	C.1	phylogeny
EPI_ISL_18228631	GISAID	2023-07-21	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_18213375	GISAID	2023-06-19	People's Republic of China	Human	IIb	C.1	phylogeny
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EPI_ISL_18702235	GISAID	2023-10-02	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_19001887	GISAID	2024-01-25	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_17809521	GISAID	2023-06-15	People's Republic of China	Human	IIb	C.1	phylogeny
EPI_ISL_18075506	GISAID	2023-05-01	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_17665624	GISAID	2023-04-17	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_18097375	GISAID	2023-05-02	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_17817240	GISAID	2023-05-19	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_17592667	GISAID	2023-04-06	Japan	Human	IIb	C.1	phylogeny
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EPI_ISL_18414668	GISAID	2023-09	USA	Human	IIb	C.1	phylogeny
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EPI_ISL_19002300	GISAID	2024-03-07	Netherlands	Human	IIb	C.1	phylogeny
EPI_ISL_18147347	GISAID	2023-04-22	South Korea	Human	IIb	C.1	phylogeny
EPI_ISL_18744050	GISAID	2023-05-03	South Korea	Human	IIb	C.1	phylogeny
EPI_ISL_17592666	GISAID	2023-04-04	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_17445518	GISAID	2023-03-31	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_18147350	GISAID	2023-04-25	South Korea	Human	IIb	C.1	phylogeny
EPI_ISL_16905444	GISAID	2022-10	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_17152843	GISAID	2023-02	Taiwan	Human	IIb	C.1	phylogeny
EPI_ISL_17428286	GISAID	2023-03	Taiwan	Human	IIb	C.1	phylogeny
EPI_ISL_17152764	GISAID	2023-03	Taiwan	Human	IIb	C.1	phylogeny
EPI_ISL_18147336	GISAID	2023-04-22	South Korea	Human	IIb	C.1	phylogeny
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EPI_ISL_18147361	GISAID	2023-04-17	South Korea	Human	IIb	C.1	phylogeny
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EPI_ISL_18147334	GISAID	2023-04-13	South Korea	Human	IIb	C.1	phylogeny
EPI_ISL_18147360	GISAID	2023-04-11	South Korea	Human	IIb	C.1	phylogeny
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EPI_ISL_18147363	GISAID	2023-04-18	South Korea	Human	IIb	C.1	phylogeny
EPI_ISL_18436040	GISAID	2023-10-12	Indonesia	Human	IIb	C.1	phylogeny
EPI_ISL_18467807	GISAID	2023-10-30	Indonesia	Human	IIb	C.1	phylogeny
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EPI_ISL_17246659	GISAID	2023-02-13	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_17428283	GISAID	2023-03	Taiwan	Human	IIb	C.1	phylogeny
EPI_ISL_17445519	GISAID	2023-03-31	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_17692268	GISAID	2023-04-28	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_17837267	GISAID	2023-06-12	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_17959214	GISAID	2023-05-11	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_17518107	GISAID	2023-03-17	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_17762485	GISAID	2023-05-17	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_17959215	GISAID	2023-05-11	Japan	Human	IIb	C.1	phylogeny

Accession number	Source	Date of collection	Country	Host	Clade	Lineage	Analysis
EPI_ISL_17959216	GISAID	2023-05-12	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_17665625	GISAID	2023-04-18	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_17592665	GISAID	2023-04-03	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_17008295	GISAID	2023-01-30	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_18147345	GISAID	2023-04-10	South Korea	Human	IIb	C.1	phylogeny
EPI_ISL_18147348	GISAID	2023-04-18	South Korea	Human	IIb	C.1	phylogeny
EPI_ISL_18147349	GISAID	2023-04-22	South Korea	Human	IIb	C.1	phylogeny
EPI_ISL_17008296	GISAID	2023-02-09	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_18147342	GISAID	2023-04-15	South Korea	Human	IIb	C.1	phylogeny
EPI_ISL_17837266	GISAID	2023-06-02	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_17445516	GISAID	2023-03-28	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_18352304	GISAID	2023-09-14	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_18147346	GISAID	2023-04-25	South Korea	Human	IIb	C.1	phylogeny
EPI_ISL_17008293	GISAID	2023-01-25	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_17592670	GISAID	2023-04-11	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_17665626	GISAID	2023-04-19	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_17246657	GISAID	2023-01-23	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_18147351	GISAID	2023-04-21	South Korea	Human	IIb	C.1	phylogeny
EPI_ISL_18697752	GISAID	2023-12-11	Cambodia	Human	IIb	C.1	phylogeny
EPI_ISL_18147359	GISAID	2023-04-12	South Korea	Human	IIb	C.1	phylogeny
EPI_ISL_18055899	GISAID	2023-06-26	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_18147355	GISAID	2023-03-13	South Korea	Human	IIb	C.1	phylogeny
EPI_ISL_18557816	GISAID	2023-09-22	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_18557818	GISAID	2023-10-25	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_18075507	GISAID	2023-05-01	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_17817241	GISAID	2023-05-20	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_17817239	GISAID	2023-05-15	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_17837268	GISAID	2023-06-09	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_17665627	GISAID	2023-04-21	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_18055900	GISAID	2023-06-26	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_17692269	GISAID	2023-04-28	Japan	Human	IIb	C.1	phylogeny
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EPI_ISL_18352306	GISAID	2023-09-19	Japan	Human	IIb	C.1	phylogeny
EPI_ISL_18059184	GISAID	2023-07-03	People's Republic of China	Human	IIb	C.1	phylogeny
EPI_ISL_18659846	GISAID	2023-11-07	Netherlands	Human	IIb	C.1	phylogeny
EPI_ISL_18702225	GISAID	2023-10-06	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_18702257	GISAID	2023-10-31	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_18059183	GISAID	2023-06-28	People's Republic of China	Human	IIb	C.1	phylogeny
EPI_ISL_18059182	GISAID	2023-06-27	People's Republic of China	Human	IIb	C.1	phylogeny
EPI_ISL_18076380	GISAID	2023-07-07	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_18553846	GISAID	2023-08-21	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_18553847	GISAID	2023-08-08	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_18702208	GISAID	2023-10-17	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_18702253	GISAID	2023-10-19	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_18702234	GISAID	2023-10-29	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_18044983	GISAID	2023-06-20	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_18702241	GISAID	2023-10-03	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_18553835	GISAID	2023-07-18	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_18553816	GISAID	2023-07-13	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_18076389	GISAID	2023-07-07	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_18553833	GISAID	2023-08-10	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_18228633	GISAID	2023-07-19	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_18634755	GISAID	2023-10	Ireland	Human	IIb	C.1	phylogeny
EPI_ISL_18228640	GISAID	2023-07-26	Portugal	Human	IIb	C.1	phylogeny
EPI_ISL_18746885	GISAID	2023-12-19	Netherlands	Human	IIb	C.1	phylogeny
EPI_ISL_18781817	GISAID	2023-10-14	USA	Human	IIb	C.1	phylogeny
EPI_ISL_18634756	GISAID	2023-10	Ireland	Human	IIb	C.1	phylogeny
EPI_ISL_18308397	GISAID	2023-08-18	Ireland	Human	IIb	C.1	phylogeny
EPI_ISL_18308399	GISAID	2023-08-28	Ireland	Human	IIb	C.1	phylogeny
EPI_ISL_18308398	GISAID	2023-08-31	Ireland	Human	IIb	C.1	phylogeny
EPI_ISL_18308396	GISAID	2023-08-16	Ireland	Human	IIb	C.1	phylogeny
EPI_ISL_18553837	GISAID	2023-07-15	Portugal	Human	IIb	C.1	phylogeny

Accession number	Source	Date of collection	Country	Host	Clade	Lineage	Analysis
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Accession number	Source	Date of collection	Country	Host	Clade	Lineage	Analysis
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OR035728.1	GenBank	2022-10-28	Belgium	Human	IIb	C.1	phylogeny
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LC760461.1	GenBank	2023-02-13	Japan	Human	IIb	C.1	phylogeny
OQ581853.1	GenBank	2023-02	Taiwan	Human	IIb	C.1	phylogeny
OQ581855.1	GenBank	2023-03	Taiwan	Human	IIb	C.1	phylogeny
LC756922.1	GenBank	2023-01-25	Japan	Human	IIb	C.1	phylogeny
LC756924.1	GenBank	2023-01-30	Japan	Human	IIb	C.1	phylogeny
LC756925.1	GenBank	2023-02-09	Japan	Human	IIb	C.1	phylogeny
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EPI_ISL_19108156	GISAID	2023-10-16	Vietnam	Human	IIb	C.1	intra-host mutation
EPI_ISL_19108157	GISAID	2023-10-11	Vietnam	Human	IIb	C.1	intra-host mutation
EPI_ISL_19108158	GISAID	2023-10-19	Vietnam	Human	IIb	C.1	intra-host mutation

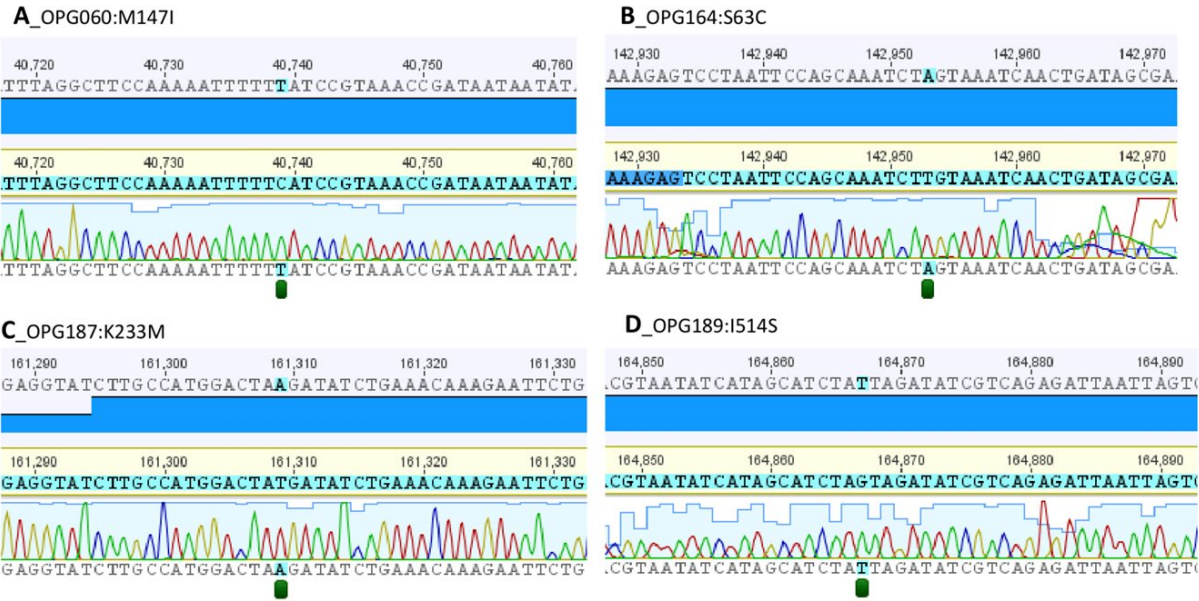


**Appendix Figure 1.** Novel nonsynonymous substitutions documents in 14 sequences of the present study. Notes to Appendix Figure 1: E: Glutamate, K: Lysine, D: Aspartate, Y: Tyrosine, S: Serine, N: Asparagine, T: Threonine, L: Leucine, P: Proline, A: Alanine and I: Isoleucine

## OPG068:S428L



**Appendix Figure 2.** Representative of Sanger sequencing results confirming the presence of the novel APOBEC3-like mutation (OPG068: S428L) in the original samples.



**Appendix Figure 3.** Screen shots showing results of Sanger sequencing reads aligned to corresponding metagenomic reads (cyan) obtained from longitudinal samples. Positions with potential nucleotide substitutions leading to amino acid changes observed in metagenomics datasets are highlighted. The discrepancy between Sanger and Metagenomics reads means substitutions were not confirmed by Sanger sequencing. Otherwise, great agreements between the two methods were achieved, especially despite low sequencing coverage obtained from metagenomics reads carrying the two nonsynonymous substitutions (Ile to Met and Ser to Cys shown in Appendix Table 7).