Full-length genome characterization and phylogenetic analysis of SARS-CoV-2 virus strains from Indonesia

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Research Article

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Abstract

Background: Recently, SARS-CoV-2 virus with the D614G mutation has become a public concern due to rapid dissemination of this variant across many countries. Our study aims were 1) to report full-length genome sequences of SARS-CoV-2 collected from four COVID-19 patients in the Special Region of Yogyakarta and Central Java provinces, Indonesia; 2) to compare the clade distribution of full-length genome sequences from Indonesia (n=60) from March to September 2020; and 3) to perform phylogenetic analysis of SARS-CoV-2 complete genomes from different countries, including Indonesia.

Methods: Whole genome sequencing (WGS) was performed using next-generation sequencing (NGS) applied in the Illumina MiSeq instrument**.** Full-length virus genomes were annotated using the reference genome of hCoV-19/Wuhan/Hu-1/2019 (NC_045512.2) and then visualized in UGENE v. 1.30. For phylogenetic analysis, a dataset of 88 available SARS-CoV-2 complete genomes from different countries, including Indonesia, was retrieved from GISAID.

Results: All patients were hospitalized with various severities of COVID-19. Phylogenetic analysis revealed that one and three virus samples belong to clade L and GH. These three clade GH virus samples (EPI_ISL_525492, 516800 and 516829) were not only located in a cluster with SARS-CoV-2 genomes from Asia but also those from Europe, whereas the clade L virus sample (EPI_ISL_516806) was located amongst SARS-CoV-2 genomes from Asia. Using full-length sequences available in the GISAID EpiCoV Database, 39 of 60 SARS-CoV-2 (65%) from Indonesia harbor the D614G mutation.

Conclusion: These findings indicate that SARS-CoV-2 with the D614G mutation appears to become the major circulating virus in Indonesia, concurrent with the COVID-19 situation worldwide.

Introduction

In December 2019, an outbreak of severe acute respiratory syndromecoronavirus-2 (SARS-CoV-2) causing Coronavirus disease 2019 (COVID-19) was detected in Wuhan, China and has become a global pandemic, including Indonesia [1,2].

Since it was first announced in Indonesia on March 2020, COVID-19 cases have increased rapidly over time, thus requiring continued attention. On September 21, 2020, Indonesia recorded 248,852 COVID-19 infections and 9,677 deaths [3]. Recently, SARS-CoV-2 with the D614G mutation became the major frequency globally. Interestingly, SARS-CoV-2 with the G614 variant had significantly higher infectious titers than the original D614 virus, and COVID-19 patients with the G614 variant had a higher viral load than patients without the mutation. However, this mutation was not associated with the severity of COVID-19 [4]. Here, we aimed 1) to report full-length genome sequences of SARS-CoV-2 collected from four COVID-19 patients in the Special Region of Yogyakarta and Central Java provinces, Indonesia; 2) to compare the clade distribution of full-length genome sequences from Indonesia (n=60) from March to September 2020; and 3) to perform phylogenetic analysis of SARS-CoV-2 complete genomes from different countries, including Indonesia.

Methods

Virus samples

Four virus samples were collected from hospitalized patients with COVID-19 from June-August 2020 in Yogyakarta and Central Java provinces. Samples were collected from nasopharyngeal swabs and then directly put into viral transport media (VTM). Samples were sent to the Department of Microbiology and Laboratorium Diagnostik Yayasan Tahija World Mosquito Program, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada and the Disease Investigation Center, Wates, Yogyakarta for SARS-CoV-2 virus detection using real-time reverse transcription polymerase chain reaction (RT-PCR).

Whole genome sequencing

Total viral RNA was extracted from original samples (nasopharyngeal swabs) using a QiAMP Viral RNA mini kit (Qiagen, Hilden, Germany), followed by double stranded cDNA synthesis using Maxima H Minus Double-Stranded cDNA Synthesis (Thermo Fisher Scientific, Massachusetts, United States), and then purified by a GeneJET PCR Purification Kit (Thermo Fisher Scientific, Massachusetts, United States). The Nextera DNA Flex for Enrichment using Respiratory Virus Oligos Panel was used for library preparations, and whole genome sequencing (WGS) was performed using next generation sequencing (NGS) applied in the Illumina MiSeq instrument (Illumina, San Diego, US) with Illumina MiSeq reagents v3 150 cycles (2 x 75 cycles). The paired reads were trimmed for quality and length and assembled by mapping to the reference genome from Wuhan, China (hCoV-19/Wuhan/Hu-1/2019, GenBank accession number: NC_045512.2) using BWA or Bowtie sequence alignment methods in UGENE v. 1.30 [5]. All four full-genome sequences of SARS-CoV-2 had the following accession IDs: EPI_ISL_516800, EPI_ISL_516806, EPI_ISL_516829, and EPI_ISL_525492 [6].

Genome annotation and phylogenetic analysis

Full-length virus genomes were annotated using the reference genome of hCoV-19/Wuhan/Hu-1/2019 (NC_045512.2) and then visualized in UGENE v. 1.30 [5].

For phylogenetic analysis, a dataset of 88 available SARS-CoV-2 complete genomes from different countries, including Indonesia, was retrieved from GISAID (Acknowledgment Table provided in Supplementary Data). Sequence alignment was performed using the MAFFT program server for multiple nucleotide sequence alignment (https://mafft.cbrc.jp/alignment/server/). A phylogenetic tree was constructed from 29.400 nt length of the open reading frame (ORF) of SARS-CoV-2 using the neighbor-joining (NJ) statistical method with 2000 bootstrap replications. Since base pair changes by transitions were more frequently observed than those by transversions in the SARS-CoV-2 genome [7], we used the Kimura-2 parameter model for the nucleotide substitution model using uniform rates among sites and pairwise deletion for gap treatment. All phylogenetic reconstructions were performed in MEGA 7.0 [8].

Ethical Approval

The Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito Hospital approved this study (KE/FK/0563/EC/2020). Written informed consent was obtained from all participants before joining in this study.

Results

Whole genome sequences of SARS-CoV-2 from the Special Region of Yogyakarta and Central Java provinces, Indonesia

Case 1

An 83-year-old female patient complained of fever 13 days before admission. She had a history of contact with a COVID-19 confirmed case, and RT-PCR tests were conducted on August 10, 2020, with positive results. She had comorbidities of hypertension, geriatric syndrome, and congestive heart failure. The physical examination recorded a blood pressure of 150/90 mmHg, with normal results on her remaining vital signs. Chest X-rays showed the appearance of infiltrate on both lungs. She was diagnosed with moderate COVID-19 and mild pneumonia. After admission, the patient received antibiotics and antiviral therapy based on the COVID-19 Prevention and Control guidelines by the Indonesian Ministry of Health, namely, azithromycin and oseltamivir. The patient was uneventfully discharged from the hospital 29 days after admission. Whole genome sequencing revealed that the virus sample collected from this patient (hCoV19/Indonesia/YO-781481/2020, ID: EPI_ISL_516829) belonged to the GH clade with 9 amino acid mutations in 6 proteins, including NSP3 (P679S), NSP12 (P323L, A656S), NSP13 (M576I), spike (D614G), NS3 (A54V, Q57H, A99S), and NP (Q160R) (Table 1; Fig. 1).

Case 2

A 77-year-old male patient complained of dry cough. He had a history of contact with a COVID-19 confirmed case two weeks before admission. RT-PCR tests were conducted on June 22, 2020, with positive results. He had a comorbidity of gout arthritis. The physical examination recorded a blood pressure of 120/80 mmHg, pulse of 68 per minute, respiratory rate of 20 per minute, body temperature of 36.6°C, and oxygen saturation of 95% with room air. Lung auscultation revealed crackles posteroinferior to the lung. Chest X-rays showed no abnormality, but thoracic CT scan revealed infiltrate and ground glass opacities on the bilateral posteroinferior lung, typical of viral pneumonia caused by COVID-19 infection. We found increases in the NLR and uric acid of 3.11 and 8.9 mg/L, respectively. He was diagnosed with moderate COVID-19 and mild pneumonia. The patient received azithromycin and hydroxychloroquine. He was uneventfully discharged from the hospital 20 days after admission. Whole genome sequencing revealed that virus samples collected from this patient (hCoV19/Indonesia/YO-202449/2020, ID: EPI_ISL_516800) belonged to the GH clade with 4 amino acid mutations in 4 proteins: NSP3 (P822L), NSP12 (P323L), Spike (D614G), and NS3 (Q57H) (Table 1; Fig. 1).

Case 3

A 55-year-old female presented with complaints of cough that were experienced from one week before admission. Positive RT-PCR results were obtained on June 26, 2020. The patient had comorbidities of diabetes mellitus. Her vital signs are within normal limits. Lung auscultation revealed crackles in both lungs. Chest X-rays showed bilateral infiltrate. We found increases in blood glucose levels of 340.56 mg/dL. A blood culture test was performed and showed negative bacterial growth. She was diagnosed with moderate COVID-19 and mild pneumonia. The patient received antibiotics and antiviral therapy concordant with the COVID-19 Prevention and Control guidelines by the Indonesian Ministry of Health, namely, azithromycin, hydroxychloroquine, and oseltamivir. She uneventfully recovered and was discharged from the hospital 31 days after admission. Whole genome sequencing revealed that virus samples collected from this patient (hCov19/Indonesia/JT-202538/2020, ID: EPI_ISL_525492) belonged to the GH clade with 5 amino acid mutations in 5 proteins: NSP3 (P822L), NSP12 (P323L), Spike (D614G), NS3 (Q57H), and NS7a (H73Y) (Table 1; Fig. 1).

Case 4

A 30-year-old male came to the emergency department with a chief complaint of cough. His experienced sore throat and coughing up mucoid phlegm. The RT-PCR tests on SARS-CoV-2 upon admission were positive (conducted on May 16, 2020). His vital signs are within the normal range.

Pulmonary auscultation was unremarkable. Chest X-rays showed no abnormality, while routine blood tests revealed lymphopenia. He had a history of traveling from the local COVID-19 transmission area. He was diagnosed with mild COVID-19. The patient received guideline-based therapy, namely, hydroxychloroquine and oseltamivir. The patient was discharged from the hospital 30 days after admission. Whole genome sequencing revealed that virus samples collected from this patient (hCoV19/Indonesia/YO-200927/2020, ID: EPI_ISL_516806) revealed the L clade with only one mutation in the NSP5 protein (M49I) (Table 1; Fig. 1).

Table 1. Characteristics of four patients with COVID-19 and SARS-CoV-2 virus samples from Yogyakarta and Central Java.

Patient No	Sex	Age (yo)	COVID-19 severity	C_T value	Virus name (ID)	Collection Date	Lineage/clade (GISAID)	Amino acid mutation* (no. mutation and position of proteins-*encoded genes*)	Nucleotide variations in untranslated regions (position of nucleotide)
1	Female	83	Moderate	16.9	hCoV19/Indonesia/YO-781481/2020 (EPI_ISL_516829)	10/08/2020	B.1.36 (GH)	9: **NSP3**-*ORF1ab* (P679S), **NSP12**-*ORF1ab* (P323L, A656S), **NSP13**-*ORF1ab* (M576I), **Spike**-*S* (D614G), **NS3**-*ORF3a* (A54V, Q57H, A99S), **NP**-*N* (Q160R)	5'-UTR: 241 C à T
2	Male	77	Moderate	19.7	hCoV19/Indonesia/YO-202449/2020 (EPI_ISL_516800)	22/06/2020	B.1.36 (GH)	4: **NSP3**-*ORF1ab* (P822L), **NSP12**-*ORF1ab* (P323L), **Spike**-*S* (D614G), **NS3**-*ORF3a* (Q57H)	5'-UTR: 241 C à T
3	Female	55	Moderate	24.7	hCov19/Indonesia/JT-202538/2020 (EPI_ISL_525492)	26/06/2020	B.1.36 (GH)	5: **NSP3**-*ORF1ab* (P822L), **NSP12**-*ORF1ab* (P323L), **Spike**-*S* (D614G), **NS3**-*ORF3a* (Q57H), **NS7a**-ORF7a (H73Y)	5'-UTR: 26 A à G, 241 C à T
4	Male	30	Mild	27.9	hCoV19/Indonesia/YO-200927/2020 (EPI_ISL_516806)	16/05/2020	B (L)	1: **NSP5**-*ORF1ab* (M49I)	5'-UTR: 22 A à G, 23 G à A 3'-UTR: 29685 T à A

* Name of protein (bold) is followed by encoded gene (italic) and amino acid mutation in bracket

C_T, cycle threshold

Ref. sequence: hCoV-19/Wuhan/Hu-1/2019 (NC_045512.2)

Clade distribution of full-length genome sequences from Indonesia

Whole genome sequencing revealed that one virus (hCoV19/Indonesia/YO-202449/2020, EPI_ISL_516800) had a complete SARS-CoV-2 genome (29.903 nt). Although the other three virus samples were shorter due to incomplete UTRs at either the 5' or 3', they possessed full-length and complete open reading frames (ORFs) with a size of 29.409 nt consisting of 11 genes (ORF1ab, S, ORF3a, E, M, ORF6, ORF7a, ORF7b, ORF8, N, ORF10) (Fig. 1).

Next, we compared the clade distribution of full-length genome sequences from Indonesia (n=60) from March to September 2020. Based on the collection data, most (39/60, 65%) virus genomes contained the D614G mutation representing clade G (2), GR (7), and GH (30) (Fig. 2). From March to April 2020, clade L was dominant. On the other hand, there has been an increase in the detection of clade GH since April 2020 until now.

Phylogenetic analysis

Phylogenetic analysis of whole genome sequencing showed that three virus samples (EPI_ISL_525492, EPI_ISL_516800 and EPI_ISL_516829) belonged to the clade GH clade and were located amongst SARS-CoV-2 viruses from Asia (Indonesia, Vietnam, China, Singapore, South Korea, Saudi Arabia, India, Japan) and Europe (England and Italy) (Fig. 3). On the other hand, one virus sample (EPI_ISL_516806) belonged to clade L and was located in a cluster with g SARS-CoV-2 virus mainly from Asia (Wuhan, Malaysia, Indonesia, India, United Arab Emirates, and Japan) (Fig. 3)

Discussion

Based on the data available in GISAID, 60 virus samples representing five clades have been detected from COVID-19 in Indonesia up to September 2020 (based on full-length genome and collection time): L (20), O (1), G (2), GR (7), and GH (30) [6]. Here, we report four full genomes of SARS-CoV-2 from patients with COVID-19 in Yogyakarta and Central Java Provinces, Indonesia. All the samples were classified within GH clades, except one. This finding corresponds with the situation in Indonesia, showing that during the early pandemic in March-April, only two clades, O and L, were detected, with the latter clade (L) more dominantly found from COVID-19 cases. However, since the first detection of clade GH in April 2020, this virus was more frequently detected than the other clades. Whether this correlates with the increase in the number of COVID-19 recently in Indonesia has to be investigated further. Interestingly, a similar situation was found in some countries in North America and Africa, which also detected more SARS-CoV-2 virus strains belonging to clade GH than to the other clades. An increase in SARS-CoV-2 detection conveys the D614G mutation concurrent with the recent global situation of COVID-19 [6].

One of the patients revealed the L clade. The L clade is the original lineage, corresponding to the reference genome of NC_045512.2 [9]. The D614G mutation dominates globally approximately 77,818/96,215 (~81%) full genomes submitted at GISAID until September 18, 2020 [6]. Three of four (75%) SARS-CoV-2 in our case series also consisted of D614G. According to phylogenetic tree and sequence distribution analysis, it has been suggested that the dominating D614G globally is caused by a founder effect [10]. Whether the same mechanism occurs in Indonesia is difficult to conclude since only limited full genomes were submitted to GISAID until the collection date of the end of September 2020 (n=60) [6]. The virus with the D614G mutation in Indonesia was first detected on April 2020 in Surabaya, East Java [6], followed by other provinces, including Yogyakarta, Central Java, West Java and Banten. Clade L was mostly detected in Jakarta (7/20) and Surabaya, East Java (7/20), followed by Papua (3/20) (Fig. 2) [6].

It has been reported that COVID-19 patients with the D614G mutation have a higher viral load than patients infected by SARS-CoV-2 without mutations [4]. The patients with D614G had a Ct value lower than one patient without the mutation (Table 1).

Interestingly, patients infected with SARS-CoV-2 bearing D614G mutations showed moderate COVID-19, while the patient without mutations suffered from mild symptoms. These differences might be associated with the small sample size of our study (n=4) compared with previous studies (n=999 [4], 175 [9], and 88 [10]).

Among GH clades, they also consisted of different mutations in addition to the variants that determine the clade name (Table 1). It has already been reported that the D614G variant is almost always accompanied by three other variants: a C-to-T change in the 5'UTR, a silent c.3307C>T variant, and P323L [4]. All GH clade samples in the present study also contained P323L (Table 1).

Notably, whole genome sequencing is of practical importance to determine virus variants and clades and is associated with particular geographic disseminations to decide clinical and political approaches at the regional and local levels [9]. Moreover, whether the differences in the case fatality rate and viral spread or transmission among different countries/regions are affected by differences in the virus clade [13] needs to be further studied.

Conclusions

We report the full-genome sequence characterization and phylogenetic analysis of SARS-CoV-2 from Indonesia. SARS-CoV-2 with the D614G mutation appears to become the major circulating virus in Indonesia, which is concurrent with the COVID-19 situation worldwide. Further study with a larger sample size is necessary to investigate whether the dominating SARS-CoV-2 bearing the D614G mutation is due to a founder effect or other mechanism and to explore the role of the D614G mutation in the pathogenesis and virulence of SARS-CoV-2.

Declarations

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Disclaimers

No potential conflict of interest relevant to this article was reported.

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Figures

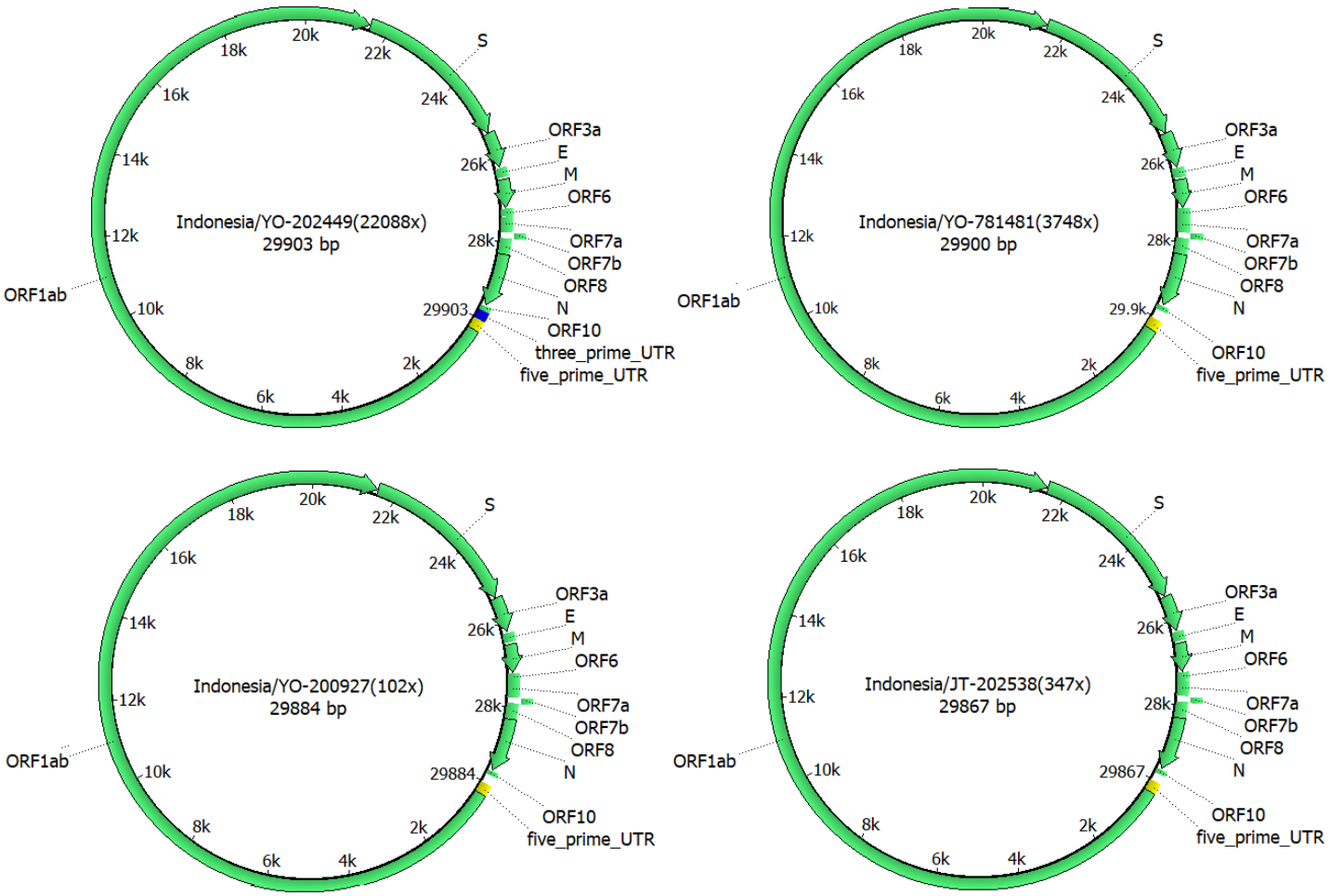

Figure 1

Circular map of four SARS-CoV-2 genomes from Yogyakarta and Central Java mapped to reference hCoV-19/Wuhan/Hu-1/2019 (NC_045512.2). The virus name is located within the map with NGS average coverage and genome length. One virus (hCoV-19/Indonesia/YO-202449/2020) had a complete SARS-CoV-2 genome (29.903 nt), while the other three possessed a full-length ORF (29.409 nt) consisting of 11 genes (ORF1ab, S, ORF3a, E, M, ORF6, ORF7a, ORF7b, ORF8, N, ORF10), but some had incomplete UTRs at either the 5' or 3' ends.

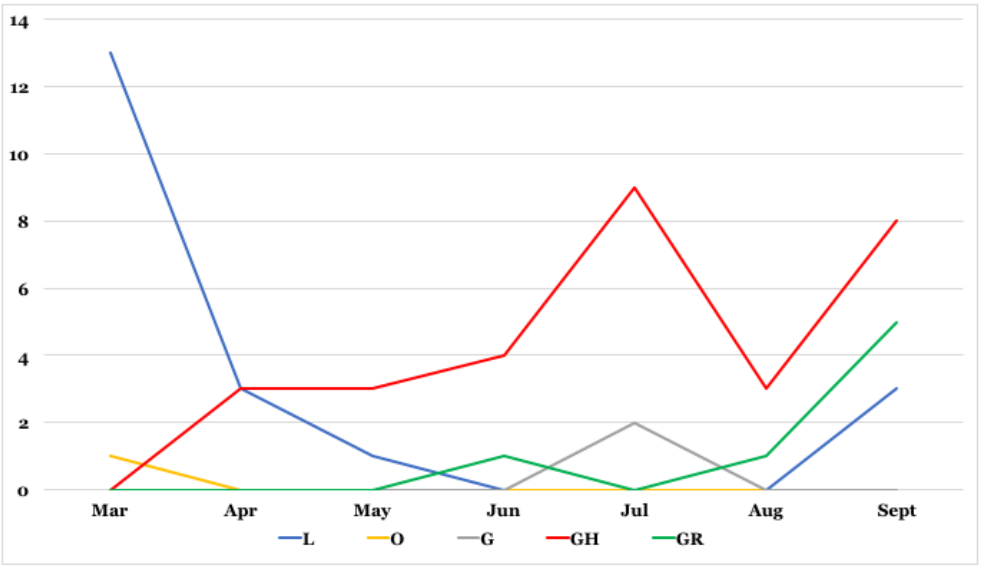

Figure 2

Clade distribution of SARS-CoV-2 genomes in Indonesia until the collection date of September 2020, showing that 65% contained the D614G mutation.

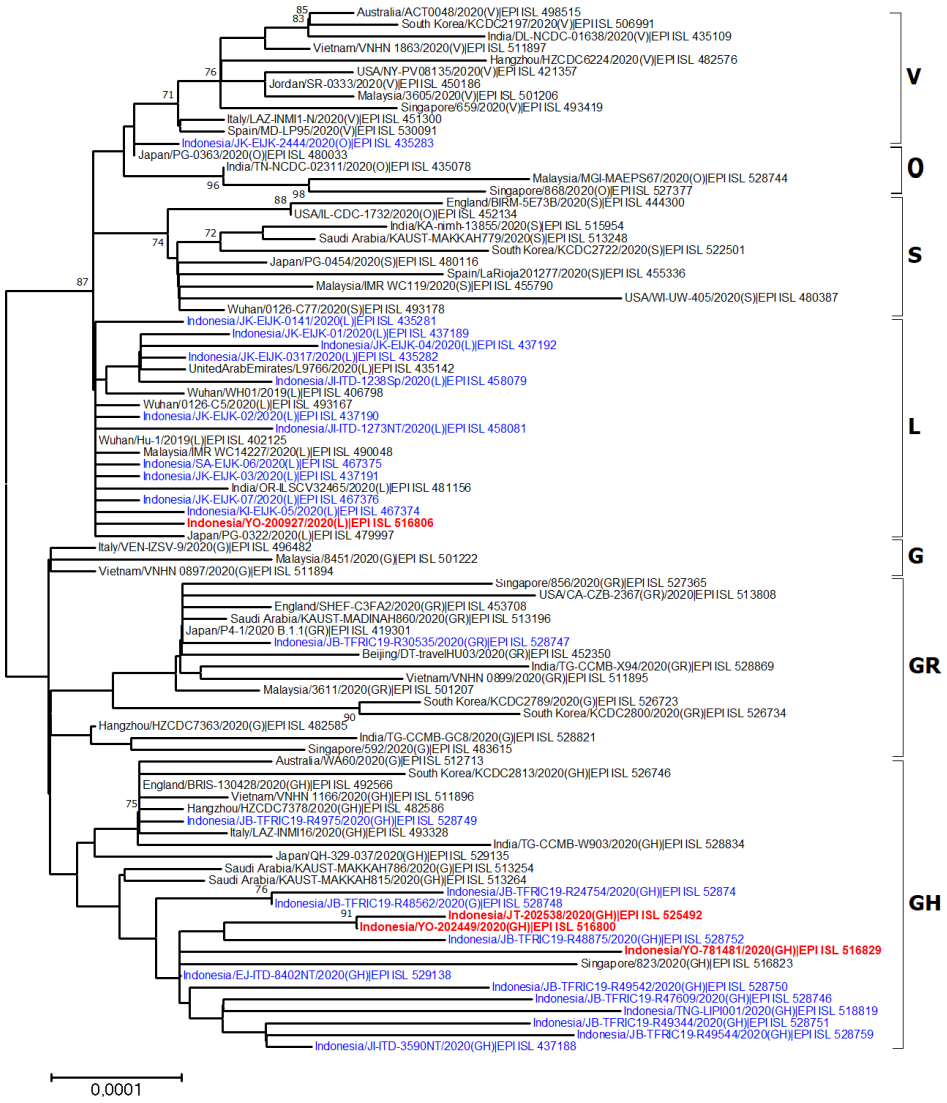

Figure 3

Phylogenetic analysis of SARS-CoV-2 genomes from Indonesia and different countries. A phylogenetic tree was constructed from 29.400 nt length of the open reading frame (ORF) of SARS-CoV-2 using the neighbor-joining (NJ) statistical method with 2000 bootstrap replications. Virus samples from Yogyakarta and Central Java are indicated in red, while those from other regions in Indonesia are indicated in blue.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplmentTableAcknowledgmentsGISAID.xlsx