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Letter to the Editor

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Recombination between SARS-CoV-2 Omicron BA.1 and BA.2 variants identified in a traveller from Nepal at the airport quarantine facility in Japan

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We conducted a sentinel genome surveillance of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with assistance from airport quarantine stations.[1] Until 14 March 2022, the whole-genome sequences of 8030 quarantine and 224 582 domestic SARS-CoV-2 isolates in Japan have been deposited in the Global Initiative on Sharing All Influenza Data (GISAID) EpiCoV database. During quarantine surveillance, by pre-entry SARS-CoV-2 screening, at international airports, we identified a unique isolate IC-5720 (collection date: 22 February 2022; GISAID ID: EPI_ISL_11057288; short-read archive: DRX340596) from a traveller visiting from Nepal, exhibiting prominent genomic recombination between the Omicron variants BA.1 and BA.2. Initially, IC-5720 was not adequately assigned as BA.2 owing to the recombination and a low-quality assignment ('not determined' or 'none') in the PANGO lineage.[2] Detailed genome alignment using the Nextclade tool suggested that despite belonging to the 21 L (Omicron, BA.2) clade, the IC-5720 isolate has mutation profiles in the whole ORF1a gene identical to those in 21 K (Omicron, BA.1). This revealed a possible breakpoint at the end of the ORF1a gene between BA.1 and BA.2 variants (Figure 1A). Heterogeneous mixed alleles were not identified during deep sequencing (2013 × mean read depth), suggesting that the isolate did not originate from a mixed infection. IC-5720 carries a spike protein identical to that in the BA.2 variant, eliminating concerns for further risks of infectivity and immune escape. Collectively, a recombinant isolate similar to IC-5720, although not entirely identical, has been identified in the UK and USA (Figures 1B and C).

Several reports have described the identification of multiple recombinant SARS-CoV-2 isolates based on the alpha variant of concern.[3,4] Recently, possible recombination between Delta and Omicron variants has also been reported. *In vitro* experiments demonstrated eight potential recombination hotspots (breakpoints) in the microhomologous sequence of the SARS-CoV-2 genome.[5] However, these hotspots were not identified within the IC-5720 isolate, suggesting a rare recombination pattern compared to that in known cases.

In conclusion, IC-5720 could have been generated via a novel recombination event between BA.1 and BA.2 variants. IC-5720 was identified at the airport quarantine station in a traveller from Nepal, indicating the possibility of similar novel recombination that might be ongoing in COVID-19 patients in Nepal and surrounding countries. Intensive monitoring during quarantine, in addition to extensive community surveillance, could aid in the early detection of novel variants that emerge in areas with limited sequencing capacity and prompt timely assessment and response to avoid global dissemination.

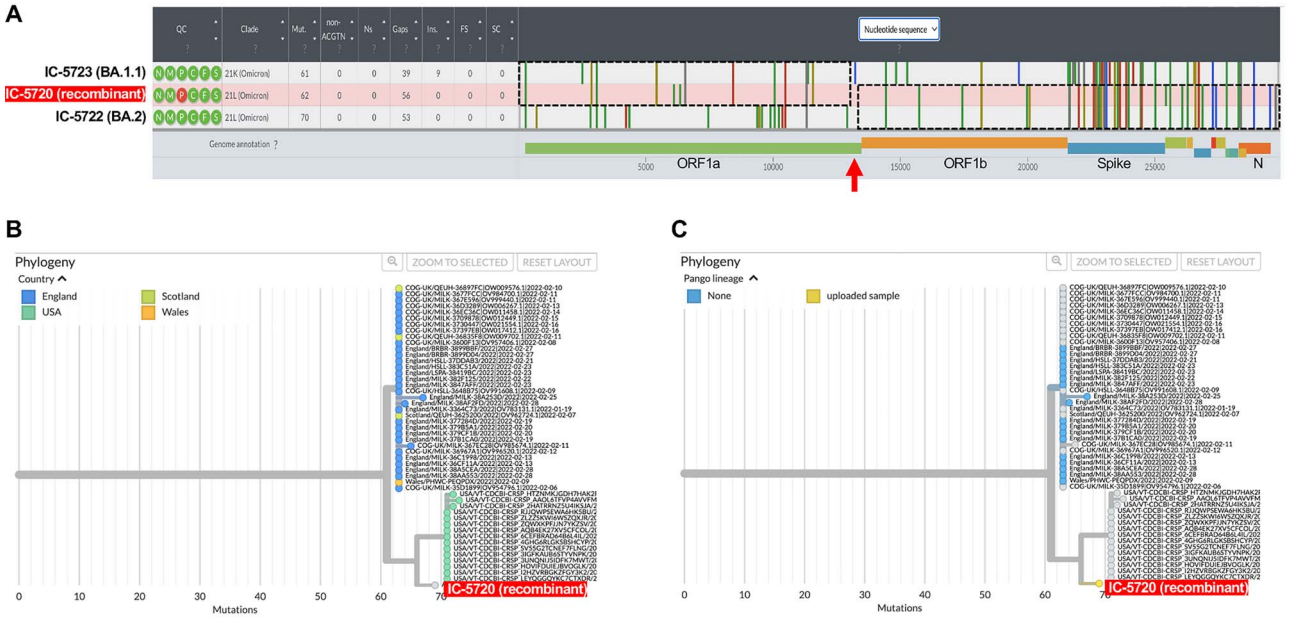

Figure 1. Clade assignment and pair-wise genome alignment of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) isolate. (A) Comparison between the control for Omicron BA.1.1 (IC-5723, EPI_ISL_11057296) and BA.2 (IC-5722, EPI_ISL_11057294). Nextclade alignment assigned the IC-5720 to isolate (highlighted in red) to the 21 L (Omicron) clade; however, the mutation profile in the *ORF1a* gene suggested a profile identical to that of BA.1.1 (EPI_ISL_11057296). Similar mutation profiles among three isolates are enclosed by a dashed line. The possible recombination breakpoint is annotated with a red arrow. Detected nucleotide variations are highlighted with a vertical line (A: red, G: brown, C: blue and T: green). (B and C) Ultrafast Sample placement on Existing tRee (UShER) analysis for IC-5720 (performed on 2022-03-14). The top 50 similar sequences were further analysed using Nextstrain to visualize the phylogenetic relationship in the country (B) and Phylogenetic Assignment of Named Global Outbreak (PANGO) lineage (C).

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Ethics statement

The study protocol was approved by the National Institute of Infectious Diseases, Japan (approval no. 1091). The Ethics Committee waived the requirement for written consent for research on viral genome sequences.

Conflict of interests

None declared.

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