The current pandemic of COVID-19 is fueled by more infectious emergent Omicron variants. Ongoing concerns of emergent variants include possible recombinants, as genome recombination is an important evolutionary mechanism for the emergence and re-emergence of human viral pathogens. In this study, we identified diverse recombination events between two Omicron major subvariants (BA.1 and BA.2) and other variants of concern (VOCs) and variants of interest (VOIs), suggesting that co-infection and subsequent genome recombination play important roles in the ongoing evolution of SARS-CoV-2. Through scanning high-quality completed Omicron spike gene sequences, 18 core mutations of BA.1 (frequency >99%) and 27 core mutations of BA.2 (nine more than BA.1) were identified, of which 15 are specific to Omicron. BA.1 subvariants share nine common amino acid mutations (three more than BA.2) in the spike protein with most VOIs, suggesting a possible recombination origin of Omicron from these VOIs. There are three more Alpha-related mutations in BA.1 than BA.2, and BA.1 is phylogenetically closer to Alpha than other variants. Revertant mutations are found in some dominant mutations (frequency >95%) in the BA.1. Most notably, multiple characteristic amino acid mutations in the Delta spike protein have been also identified in the “Deltacron”-like Omicron Variants isolated since November 11, 2021 in South Africa, which implies the recombination events occurring between the Omicron and Delta variants. Monitoring the evolving SARS-CoV-2 genomes especially for recombination is critically important for recognition of abrupt changes to viral attributes including its epitopes which may call for vaccine modifications.
Tracking SARS-CoV-2 Omicron diverse spike gene mutations identifies... Ou et al.

RESULTS
The common mutations among Omicron (BA.1 and BA.2) and variants of concern (VOCs) proposed in this study were investigated the spike diversity of the Omicron variants along with the shared spike mutations between Omicron and other variants of concern (VOCs) and variants of interest (VOIs). The Omicron spike amino acid sequences archived during the early transmission phase, and released in the GISAID database (submitted before 15 January 2022) were accessed, including 52,563 high-quality Omicron spike sequences (representing 49,609 BA.1 and 2954 BA.2 sequences). We demonstrate that the emerging and circulating Omicron subvariants originate in part through recombination with other variants. We find Revertant haplotypes in the BA.1 subvariant. Most notably, multiple characteristic amino acid mutations in the Delta spike protein have been also identified in the “Deltacron”-like Omicron Variants.

Novel mutations and mutations with decreased frequency in the spike gene of Omicron BA.1 and BA.2

We investigated additional mutations among recently emerged BA.1 isolates and identified eight novel mutations in Omicron variant which were also found in other VOCs and VOIs (Table 2). For example, mutations R346K (33.90% of 49,609 BA.1 sequences) was found in Mu variants; A701V (5.50%) was found in Beta variants; LSF (0.37%) was found in lota variants; and T76I (0.10%) was found in Lambda variants. Most notably, multiple representative amino acid mutations in the Delta spike protein were also identified in the recently emerged Omicron subvariants (del156-167, R158G, L452R, and P681R, at percentages of 0.14%, 0.14%, 1.81%, and 0.12%, respectively. This implied possible recombination events between the Omicron and Delta strains during the pandemic. The first "Deltacron"-like Omicron strain was isolated on November 11, 2021 in South Africa, followed on November 23 in Botswana. This indicates that the recombination between Omicron and Delta strains may occur during the early transmission phase. The other newly noted mutations (L141F, F643L, I1081V, S1147L, and P1162S) may have originated independently (Table 2).

Several novel mutations were reported to be related to spike protein function, resulting in an enhancement of virus infectivity or in viral immune escape. Mutations that occurred in RBD, e.g., R346K, could result in a relatively weakened neutralizing antibody effect. A L452R mutation may provide evasion from cellular immunity and increased infectivity. The P681R as well as F643L and A701V mutations, near the S1/S2 cleavage site, may be associated with enhanced fusogenicity and pathogenicity of SARS-CoV-2 Delta variants. Additionally, mutations T76I, L141F, G142Y, 156–167 deletion, and R158G, located in the NTD region, were noted to affect antibody binding efficiencies and contribute to immune escape. These mutations sites are mapped and shown in Fig. 2a, b.

Apparent revertant mutations are found in some dominant mutations (frequency >95%) in the BA.1 subvariant during the pandemic. Examples are the mutations in NTD (del211 and N212I) and RBD (G339D, S373L, S373P, S375F, K417N, 440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, and Y505H). The frequency of insertions of the amino acids EPE at site 214 in BA.1 decreased during the pandemic from more than 95% on 1 December 2021 to 89% on 15 January 2022. However, BA.2 spike protein remained constant (frequency >99%), with the exception of the three amino acid deletion (LPP) found at amino acids 24–26, which decreased from more than 95% frequency on 1 December 2021 to 85% on 15 January 2022 (Table 1). This may possibly be due to selection pressure on the circulating Omicron strains.

Diverse haplotypes of Omicron spike gene and full genome phylogenetic trees show multiple recombination events during the pandemic

The spike gene of Omicron subvariants consists of 49 representative haplotypes (each occurring in more than 50 sequences). BA.1, BA.2, R346K, L452R, and A701V, and a revertant type were identified in the phylogenetic network analysis (Fig. 3a). A large number of BA.1 spike mutations delineated haplotype 2, R346K, L452R, and A701V clusters and formed distinct subgroups.
### Table 1. Comparison of Spike protein amino acid mutations between the Omicron subvariants and other VOCs and VOIs

| Spike region | Position | Mutation (BA.1) | Frequency (BA.1) | Percentage | Mutation (BA.2) | Frequency (BA.2) | Percentage | Mutation in VOCs/VOIs | New mutation |
|--------------|----------|----------------|------------------|------------|----------------|------------------|------------|----------------------|-------------|
|              |          |                |                  |            |                |                  |            |                      |             |
| NTD          | 19       | –              | –                | –          | T19I           | 2953             | 100.00%    | –                    |             |
|              | 24       | –              | –                | –          | deletion       | 2513             | 85.10%     | –                    |             |
|              | 25       | –              | –                | –          | deletion       | 2513             | 85.10%     | –                    |             |
|              | 26       | –              | –                | –          | deletion       | 2513             | 85.10%     | –                    |             |
|              | 27       | –              | –                | –          | A27S           | 2513             | 85.10%     | –                    |             |
|              | 67       | A67V           | 49,475           | 99.73%     | –              | –                | –          | –                    |             |
|              | 69       | Deletion       | 49,385           | 99.55%     | –              | –                | –          | –                    | Alpha(del69) |
|              | 70       | Deletion       | 49,382           | 99.54%     | –              | –                | –          | –                    | Alpha(del70) |
|              | 95       | T95I           | 49,513           | 99.81%     | –              | –                | –          | Mu(T95I)             |             |
| S1           | 142      | G142D          | 49,424           | 99.63%     | G142D          | 2934             | 99.36%     | –                    |             |
|              | 144      | Deletion       | 49,439           | 99.66%     | –              | –                | –          | –                    | Alpha(del144), Mu(Y144S) |
|              | 211      | Deletion       | 47,840           | 96.43%     | –              | –                | –          | Mu(Y145N)            |             |
|              | 212      | N212I          | 47,839           | 96.43%     | –              | –                | –          | –                    |             |
|              | 213      | –              | –                | –          | V213G          | 2950             | 99.90%     | –                    |             |
|              | 214      | insertE        | 44,368           | 89.44%     | –              | –                | –          | –                    |             |
|              | 339      | G339D          | 48,729           | 98.23%     | G339D          | 2953             | 99.97%     | –                    |             |
|              | 346      | R346K          | 16,819           | 33.90%     | –              | –                | –          | Mu(R346K)            | Yes         |
| RBD          | 371      | S371L          | 48,297           | 97.36%     | S371F          | 2949             | 99.86%     | –                    |             |
|              | 375      | S373P          | 48,322           | 97.41%     | S373P          | 2952             | 99.97%     | –                    |             |
|              | 376      | –              | –                | –          | T376A          | 2949             | 99.86%     | –                    |             |
|              | 405      | –              | –                | –          | D405N          | 2949             | 99.86%     | –                    |             |
|              | 408      | –              | –                | –          | R408S          | 2946             | 99.76%     | –                    |             |
|              | 417      | K417N          | 44,711           | 90.13%     | K417N          | 2952             | 99.97%     | Beta(K417N), Gamma(K417T) |             |
|              | 440      | N440K          | 46,470           | 93.67%     | N440K          | 2926             | 99.09%     | –                    |             |
|              | 446      | G446S          | 46,892           | 94.52%     | –              | –                | –          | –                    |             |
|              | 452      | L452R          | 897              | 1.81%      | –              | –                | –          | –                    | Delta(L452R) Yes |
|              | 477      | S477N          | 48,185           | 97.13%     | S477N          | 2952             | 99.97%     | –                    |             |
|              | 478      | T478K          | 48,320           | 97.40%     | T478K          | 2952             | 99.97%     | Delta(T478K)        |             |
|              | 484      | E484A          | 48,024           | 96.81%     | E484A          | 2952             | 99.97%     | Beta/Gamma/Mu (E484K) |             |
|              | 493      | Q493R          | 47,999           | 96.75%     | Q493R          | 2953             | 100.00%    | –                    |             |
|              | 496      | G496S          | 47,965           | 96.69%     | –              | –                | –          | –                    |             |
|              | 498      | Q498R          | 47,917           | 96.59%     | Q498R          | 2953             | 100.00%    | –                    |             |
|              | 501      | N501Y          | 47,933           | 96.62%     | N501Y          | 2953             | 100.00%    | Alpha/Beta/Gamma/Mu (N501Y) |             |
|              | 505      | Y505H          | 47,888           | 96.53%     | Y505H          | 2952             | 99.97%     | –                    |             |
|              | 547      | T547K          | 49,496           | 99.77%     | –              | –                | –          | –                    |             |
|              | 614      | D614G          | 49,568           | 99.92%     | D614G          | 2953             | 100.00%    | Alpha/Beta/Gamma/Delta (N501Y) |             |
| SD           | 655      | H655Y          | 49,509           | 99.80%     | H655Y          | 2953             | 100.00%    | Gamma(H655Y)        |             |
|              | 679      | N679K          | 49,523           | 99.83%     | N679K          | 2953             | 100.00%    | –                    |             |
|              | 681      | P681H          | 49,515           | 99.81%     | P681H          | 2953             | 100.00%    | Alpha/Mu (P681H), Delta (P681R) |             |
|              | 701      | A701V          | 2729             | 5.50%      | –              | –                | –          | Beta(A701V)          | Yes         |
detailed mutations defining each haplotype are listed in Supplementary Table 1).

Multiple nucleotide mutations were detected in the haplotypes compared with BA.1, e.g., haplotype 19 and the revertant subgroup (H30, 32, and 43, etc.) and BA.2. The S:L452R subgroup ("Deltacron"-like Variants) consists of different haplotypes with multiple nucleotide substitutions, indicating a possibly separate origin of S:L452R haplotypes or prior recombination events. Haplotype 25 in S:L452R subgroup, with multiple nucleotide differences compared with BA.1, could have resulted through recombination between Omicron and Delta variants, gaining the mutation S:L452R from Delta and losing multiple mutations from Omicron (Fig. 3a). Some of these "Deltacron"-like haplotypes are being tracked by the UK Health Security Agency (https://www.gov.uk/government/publications/sars-cov-2-variants-of-public-health-interest/sars-cov-2-variants-of-public-health-interest-25-february-2022) and underway to confirm by Santé publique France (https://t.co/tVAKmHRYSy). The revertant subgroup consisted of Omicron haplotypes in which several BA.1 representative mutations were lost and appeared to have reverted to the bases of the Wuhan-Hu-1 strain. Multiple nucleotide differences in other haplotypes occurred, likely as multiple independent mutation events, or

| Spike region | Position | Mutation (BA.1) | Frequency (BA.1) | Percentage | Mutation (BA.2) | Frequency (BA.2) | Percentage | Mutation in VOCs/VOIs | New mutation |
|--------------|----------|----------------|-----------------|------------|----------------|-----------------|------------|----------------------|-------------|
| FP           | 764      | N764K          | 49,046          | 98.87%     | N764K          | 2953            | 100.00%    | –                    | –           |
|              | 796      | D796Y          | 49,338          | 99.45%     | D796Y          | 2952            | 99.97%     | –                    | –           |
| S2           | 856      | N856K          | 49,488          | 99.76%     | –              | –               | –          | –                    | –           |
|              | 954      | Q954H          | 49,559          | 99.90%     | Q954H          | 2953            | 100.00%    | –                    | –           |
| HR1          | 969      | N969K          | 49,537          | 99.85%     | N969K          | 2953            | 100.00%    | –                    | –           |
|              | 981      | L981F          | 49,373          | 99.52%     | –              | –               | –          | –                    | –           |

VOCs: variants of concern, VOIs: variants of interest
52,563 high-quality Omicron spike gene sequences (49,609 BA.1 sequences, and 2954 BA.2 sequences) released before 15 January 2022 were analyzed. The mutations that have appeared in more than 800 sequences were used in this analysis.

![Fig. 1](https://example.com/fig1.png)

**Fig. 1** Spike protein amino acid mutations of the Omicron subvariants (BA.1 and BA.2) compared with mutations from the other four variants of concern (VOCs). 
(a) Venn diagram noting mutations of Omicron (BA.1) and those of VOCs. 
(b) Venn diagram of Omicron (BA.2) mutations compared to ones of VOCs. 
(c) Venn diagram of mutations between Omicron (BA.1) and Omicron (BA.2). 
(d) Spike protein amino acid mutation counts of Omicron subvariants (BA.1 and BA.2) compared with mutations of VOCs.
perhaps as recombination events among highly similar sequences. Bootscan analysis of Omicron spike sequences also indicated that the reversion haplotypes (H18, H39, and H44) were more similar to Delta variants when compared to typical Omicron haplotypes (Fig. 3b).

Furthermore, single nucleotide differences could also originate from recombination events among highly similar strains. Loops detected in phylogenetic networks also indicate possible recombination events among highly similar Omicron variants or subvariants (Fig.3a, c). Multiple newly detected or recent mutations in the Omicron spike gene make it possible to trace a putative mutation origin from representative mutations in VOIs or VOCs, especially the Delta variant, which suggests possible recombination events between Omicron and Delta variants (Table 2).

For further investigating the geographic distribution and genome diversity of the “Deltacron”-like variants, 897 Omicron genomic sequences of high quality containing S:L452R mutation reported for the Delta variant were analyzed (Fig.4a). “Deltacron”-like variants were mainly distributed in North America, Europe, and West Asia (Fig.4a). Whole genome annotation of amino acid mutations and phylogenetic tree corroborated the diversity among these S:L452R containing “Deltacron”-like Omicron genomes, which consist Omicron Pango sublineages BA.1, BA.1.1 (with S:R346K), BA.1.15, and BA.1.17 (Fig. 4b, c). BA.1 and BA.1.15 are the two major sublineages that acquired S:L452R mutation. The mutation profiles among whole genomes of BA.1 are diverse, and the sequences branched to diverse clades by phylogenetic analyses.

**DISCUSSION**

Virus co-infection and recombination can amplify pathogenicity, for example, the well-studied “model organism” adenovirus,14–20 and also in coronaviruses.21,22,24 SARS-CoV-2 has been shown to co-infect and recombine.31,32 In host populations with disproportionate immunocompromised conditions, such as in Africa,33 the possibility of long-term infections of SARS-CoV-2 variants may be higher than in populations otherwise healthy and/or vaccinated. For example, on 10 June 2021, a passenger on a flight from Johannesburg, South Africa to Shenzhen, China tested positive for SARS-CoV-2. The patient was found to be coinfected with two SARS-CoV-2 variants:

| Spike region | Position | New Mutation | Frequency | Percentage | First country emerging |
|--------------|----------|--------------|-----------|------------|------------------------|
| S1 –         | 5        | L5F          | 0.37%     | Iota(L5F)  | 2021.11.19 South Africa |
| NTD 76       | T76l     | 51           | 0.10%     | Lambda (T76l) | 2021.11.26 Netherlands |
| 141          | L141F    | 56           | 0.11%     | –          | 2021.11.19 South Africa |
| 142          | G142Y    | 51           | 0.10%     | –          | 2021.12.16 USA         |
| 156          | deletion | 68           | 0.14%     | Delta(del156) | 2021.12.13 USA         |
| 157          | deletion | 71           | 0.14%     | Delta(del157) | 2021.12.13 USA         |
| 158          | R158G    | 69           | 0.14%     | Delta(E158G) | 2021.12.15 USA         |
| RBD 346      | R346K    | 16819        | 33.90%    | Mu(R346K)  | 2021.11.4 Canada       |
| 452          | L452R    | 897          | 1.81%     | Delta(L452R) | 2021.11.11 South Africa |
| SD 643       | F643L    | 138          | 0.28%     | –          | 2021.11.29 Thailand    |
| 681          | P681R    | 62           | 0.12%     | Delta(P681R) | 2021.11.23 Botswana    |
| S2 –         | 701      | A701V        | 5.50%     | Beta(A701V) | 2021.11.10 South Africa |
| – 1081       | I1081V   | 351          | 0.71%     | –          | 2021.11.18 U.K.        |
| 1147         | S1147L   | 120          | 0.24%     | –          | 2021.12.13 USA         |
| 1162         | P1162S   | 60           | 0.12%     | –          | 2021.12.10 Canada      |
Beta and Delta, with the ratio of the relative abundance between the two variants maintained at 1:9 (Beta: Delta) in a 14-day period. Moreover, putative evidence of recombination in the Orf1ab and spike genes was shown. Such recombination events may not be rare, especially considering that there are hundreds of variants circulating in the general population. In USA, during November 2021 and February 2022, Helix sequenced 29,719 positive SARS-COV-2 samples and identified 20 co-infections. In French, Delta/Omicron SARS-CoV-2 co-infections were identified in seven immunocompetent and epidemiologically unrelated patients during the fifth wave of COVID-19 pandemics. These co-infections were detected by PCR assays targeting SARS-CoV-2 S:K417N and S:L452R and confirmed by whole genome sequencing. Another case report described prolonged infectious SARS-CoV-2 shedding up to 70 days from an asymptomatic immunocompromised individual with cancer. A SARS-CoV-2 isolated from her presented with four new mutations within the spike protein and also eight in structural proteins and polymerase region. The marked within-host genomic evolution of SARS-CoV-2 with continuous turnover of dominant viral variants was observed. Under reduced immune pressure or immune-suppression, long-term infections create conditions and increase the likelihood of simultaneous co-infections with multiple SARS-CoV-2 variants, and optimizing conditions for genome recombination.

Co-infections of different SARS-CoV-2 variants in the population will accelerate their evolution through recombination. Among the Omicron subvariants and VOCs, many shared mutations were identified in this study. We speculate that some of the Omicron spike protein mutations resulted from co-infections of variants. Recombination among diverse variants may have contributed to the shared presence of different mutations between the VOCs. For example, the BA.1 subvariant has three more Alpha-related mutations (del69-70, delY144) than BA.2, and therefore may be phylogenetically closer to the Alpha variant, suggesting that Alpha or other unknown variants that carry these mutations may have contributed to the emergence of the BA.1 subvariant (Table 1). Multiple mutation differences causing reversion haplotypes may have originated from the recombination between the Omicron and other variants (Fig. 3 and Supplementary Table 1).

Except the shared mutations, many other mutations (30 in BA.1 and 25 in BA.2) could not be accounted for among previous dominant variants (Fig. 1). Mass novel spike mutations emerged in Omicron variants at the same time are quite unusual. Previous study suggested the animal origin of Omicron variants and possible zoonotic transmission events due to the Omicron mutation types. The zoonotic transmission events from deer to human and minks to human were identified, indicating that the risk of zoonotic transmission actually exists. The Spike mutation Q493R and Q498R were reported in infected mice, but rare in human. The selection pressure in animals may cause mass novel mutations in early Omicron variants, which are subsequently selected in human under selection pressure. This is confirmed by our finding that the frequency of some original BA.1 mutations has decreased during the circulation (Table 1). As previous research reported, Omicron variants seem to have more waning clinic outcomes and lower replication capacity in vitro. The unusual superiority of Omicron variants to compete the Delta variants may be due to its immune escape ability. It was previously reported that evolution of SARS-CoV-2 in an immunosuppressed...
selected by subsequent pressure from herd immunity. The ability of immune escape from pre-existing antibodies may drive the variant evolution.

A recently reported recombinant SARS-CoV-2 “Deltacron”, and its genome sequences, elicited controversy and concerns of sequencing errors and sample contamination. Nevertheless, it was confirmed that co-infections by Omicron and Delta variants have already occurred in specific populations (https://www.gov.uk/government/publications/sars-cov-2-variants-of-public-health-interest/sars-cov-2-variants-of-public-health-interest-11-february-2022). Recombination among the extant variants may lead to the emergence of new variants. A total of 10 cases of “Deltacron” are underway to be confirmed by Santé publique France (SPF) (https://t.co/TVKmHerY5p). Recently, two independent cases of infection by a Del/Omicron recombinant virus were identified in USA. In our study, multiple VOC and VOI mutations were detected in Omicron variants circulating before 15 January 2022 (Fig. 1 and Table 1). The integration of these mutations may lead to changes in phenotype. Five additional typical amino acid mutations in Delta variants were also identified in recently emergent Omicron isolates (before 15 January 2022) (Table 2).

Although the frequency of “Deltacron”-like sequences (with S:L452R mutation) increases during the pandemic, from 1937 on 15 January 2022 when the data were collected, to 6727 on 24 March 2022, the percentage of “Deltacron”-like sequences remains still low (lower than 1%). The S:L452R mutation may increase the adaption ability of “Deltacron”-like variants compared to the original Omicron variants due to its increasing immune escape. However, the competition of the virus transmission may depend on many factors. For example, the Omicron BA2 subvariant occurred later and remains low frequency before 15 January 2022, but it now exceeds BA1 subvariant in many continents in March 2022 (Supplementary Fig. 1). Omicron BA2 subvariants carry 27 core mutations in spike compared to 18 core mutations for BA1 (Table 1 and Supplementary Fig. 2). Single mutation integration of Omicron BA1 subvariants may be not enough to compete the BA2 subvariant with more mutations. Another reason is the vaccine-induced or preexisting immunity promotes the variants with stronger immune evasion dominant. In general, the wide-reaching infection is associated with not only the virus infectivity but the immune escape ability. Interestingly, we also detected more than 100 BA2 sequences with S:L452R mutation. The influence of these recombinated variants remains further monitoring.

S:R346K mutation, previously reported in Mu variants, is also identified in Omicron BA1 variants (named as Omicron BA1.1) (Tables 1, 2) with higher frequency than the early BA1 variant (Supplementary Fig. 1). This mutation is related to virus immune escape and may increase the viral adaption. S:A701V mutation related to Beta variants was also identified in Omicron variants. It may increase the cleavage efficiency of furin.

Beyond the spike gene focused in this study, we further detected possible recombination events in other genes among Omicron and Delta variants. For example, typical nucleocapsid protein (N) mutations from Delta variants were also detected within nine “Deltacron”-like sequences (with S:L452R mutation), when compared to the early Omicron strains (Supplementary Fig. 2). N protein is associated with the virus pathogenesis and immunity response. Whether these mutations change the virus pathogenicity or immunity response still needs further investigation. Multiple recombination regions found in single strain suggest active diverse recombination events among the Omicron variants.

In summary, by analyzing sequences from a large number of Omicron subvariants, we identified diverse recombination events between two Omicron subvariants and several SARS-CoV-2 VOCs/VOIs, including “Deltacron”-like variants, suggesting that co-infection and subsequent genome recombination play important...
roles in the on-going evolution of SARS-CoV-2. Some of the recombination events may have led to modifications in protein function and viral fitness. Continued monitoring of SARS-CoV-2 genomes for mutations is critically important to our understanding of its evolution and impact on human health, and is also essential for the recognition of changes to viral epitopes that would require vaccine modifications. Prevention and control of the spread of SARS-CoV-2 in immunocompromised and unvaccinated populations may contribute to slowing the generation of recombinant SARS-CoV-2 variants.

**MATERIALS AND METHODS**

Omicron sequence dataset

958,062 full-length SARS-CoV-2 Omicron spike sequences and Omicron genomic sequences of high quality containing S.L452R mutation collected before January 15, 2022, were downloaded from the GISAID EpiCoV™ Database (http://www.GISAID.org). 53,056 complete high quality Omicron spike sequences were filtered for downstream analysis. The spike sequences with gaps or degenerate bases were excluded.

Sequences alignment and mutation analysis

Sequences were aligned by MAFFT version 7 online serve with default parameter (https://mafft.cbrc.jp/alignmafft/server/) and BioEdit, using Wuhan-Hu-1 (NC_045512) strain as reference.44,45 Spike amino mutations were analyzed and calculated with BioAider V1.334 using Wuhan-Hu-1 (NC_045512) strain and Omicron haplotypes as reference.4,36 D structures were constructed using Pymol 2.0 software through SARS-CoV-2 Omicron model PDB:7WBL and 7Q07.47–49 Venn diagrams were created using jvenn.50

Haplophylogenetic network and phylogenetic tree analyses

Omicron sequence haplotypes and frequency were calculated using R package tidifyst. Haplotypes with more than 5 sequences were output. Haplotypes format were output through with DnaSP 6.0,51 and a subsequent phylogenetic network was constructed using PopART software (http://popart.otago.ac.nz/index.shtml) by median-join method with epsilon 0. Mutation and Pango lineage of “Deltacron”-like variants with L452R mutation was annotated with Nextclade (https://clades.nextstrain.org).52 Phylogenetic tree analyses were conducted with IQ-TREE2, applying the maximum-likelihood method with 1000 bootstrap replicates using TIM model selected by MFP ModelFinder.53 Reference sequences and 7QO7.47 Pymol 2.0 software through SARS-CoV-2 Omicron model PDB: 7WBL and 7Q07.47–49 Venn diagrams were created using jvenn.50

Sequence recombination analysis

The spike sequences in Reversion haplotypes were analyzed compared with dominant Omicron spike haplotypes (Frequency > 1000). The spike sequences of strain Wuhan-Hu-1 was set as reference.55 Bootscans analysis was performed using Simplot software (version 3.5.1) (https://sray.med.som.jhmi.edu/SCRoftware/ SimPlot/), Kimura (2-parameter), neighboring-joining method, with window 200 bp and step 100 bp.

**DATA AVAILABILITY**

All data are available in the manuscript, the supplementary materials, or from GISAID’s EpiCoV™ Database (www.gisaid.org).

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**AUTHOR CONTRIBUTIONS**

J.O. and Q.Z. contribute to study design and manuscript writing. J.O., W.L., X.W., T.Z., B.D., P.Y., Y.R., L.Q. and Q.Z. contribute to data analysis and data visualization. W.Z., D.S., J.C., Z.L., J.W., and Q.Z. contribute to manuscript revision. All authors have read and approved the article.

**ADDITIONAL INFORMATION**

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