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# Genetic diversity of SARS-CoV-2 Omicron variants' spike gene in Vietnam

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## Abstract

The recently emerging Omicron is of prime concern because this variant has been the cause of current large outbreaks. Omicron becomes more dangerous when numerous content mutations in the Spike (S) gene lead to more than 30 substitutions of amino acids in spike protein. Omicron variant had been identified as Variants Of Concern (VOC) when it had transmission rate overtake previous VOCs. In this report, we focus on analyzing the genetic diversity of the S gene of Omicron variants in Vietnam. Our results indicate the high level of haplotype diversity when confirmed 362 haplotypes and the haplotype diversity index at 0.9160 ± 0.0037. The analysis of nucleotide diversity display nucleotide diversity at 0.0053 ± 0.0026 and recorded 318 polymorphic sites with the average number of mutations of 40 ± 9. Almost missense mutations appeared in the RBD region, and deletion and insertion occurred in the NTD region. Besides, we note conserved mutation in the S gene of Omicron in Vietnam, namely C21618T G21987A T22200G G22578A C22674T T22679C C22686T A22688G G22775A A22786C G22813T T22882G G22992A C22995A A23013C A23040G A23055G A23063T T23075C A23403G C23525T T23599G C23604A C23854A G23948T A24424T T24469A, and C25000T. Furthermore, the genetic networks of the S gene provided more correlation between infection and mutation in this gene. Ultimately, we propose the close relation between BA.2 and BA.4, BA.5 through the network, in which necessary focus T22917G (L452R), T23018G (F486V), and other novel mutations will appear in the S gene. The network provided the whole picture of Omicron variants in Vietnam, supporting the tracing of the source of a new outbreak in the future.

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**Introduction**

The COVID-19 pandemic lasted more than two years since 2019, and diverse variants of SARS-CoV-2 have emerged. In particular, Variants of Concern (VOC) are considered a collection of variants carrying mutations in the genome that increase transmission ability, inhibit the neutralization of antibodies, and escape from the immune system. Interestingly, the Spike (S) gene of SARS-CoV-2 encodes a spike protein that plays a role in the entry of the virus into the host through interaction with the hACE2 receptor (Ovsyannikova, Haralambieva *et al.*, 2020) and is the excellent target of vaccines and monoclonal antibodies (Candido, Eich *et al.*, 2022). However, the previous research indicated that the S gene has a much faster rate of nucleotide substitution (Berrio, Gartner *et al.*, 2020) and the RBD region of this gene has a more rapid mutation rate of 2 to 3 fold, respectively, compared to the mean of the genome (Chaw, Tai *et al.*, 2020). Furthermore, the S gene was positively selected during the evolution of SARS-CoV-2 (Berrio, Gartner *et al.*, 2020) to accumulate mutations favorable for viral transmission Accordingly, O'Toole *et al.* (2022) (O'Toole, Pybus *et al.*, 2022) built a database based on S gene nucleotide sequences that aim to track the nucleotide changes and classification of SARS-CoV-2. Therefore, monitoring mutations that occur in the S gene is very important (Durmaz, Abdulmajed *et al.*, 2020) in the situation of rapidly emerging new variants. Currently, nucleotide substitutions in the S gene are considered specific mutations for the extreme infectious phenotype of VOCs (Kim, Gaudreault *et al.*, 2022). Various Spike (S) mutations characterize the extreme infectious phenotype of VOCs. This gene encodes a spike protein essential for viral cell entry and targets vaccines and therapeutics such as monoclonal antibodies (Candido, Eich *et al.*, 2022). Mutations in the S gene lead to changes in the conformation of the spike protein, thus raising concerns about the neutralizing potential of antibodies and vaccine therapy (Ou, Lan *et al.*, 2022). Previous studies have shown that the VOC variants are more transmissible than the original variant, from 29% to 97% (Campbell, Archer *et al.*, 2021). Significantly, the appearance of the Delta variant is almost eliminated, breaking the achievements preventing the pandemic in some countries. Delta's rapid transmission is determined mainly by the spike protein's L452R, T478K, and E484Q N501Y mutations (Kumar, Singh *et al.*, 2021) (Fan, Hu *et al.*, 2021). In addition, some substitutions, such as E484K, D614G, and P681H/R, have also been conserved in many different VOC variants (Papanikolaou, Chrysovergis *et al.*, 2022) (Lubinski, Frazier *et al.*, 2021) . Recently, a new variant is thought to be more infectious than the Delta variant and maintains from 30 to 45 mutations in the spike protein (Wei, Shan *et al.*, 2021) (Kumar, Thambiraja *et al.*, 2022). According to PANGO Lineages, this variant belongs to lineage B.1.1.529, named Omicron by WHO and classified as a VOC variant. Since December 2021, Omicron has almost replaced Delta as the primary source of infection infections in the United States (Fall, Eldesouki *et al.*, 2022). After that, the Omicron variant became almost universally dominant and gradually replaced the previously dangerous Delta variant (Chaguza, Coppi *et al.*, 2022).

Vietnam is one of the infrequent countries that has succeeded in controlling the epidemic situation in the early stages of the pandemic outbreak in the world. Vietnam has successfully gone 99 days with no community transmission, and most cases (60%) in Vietnam are due to entry from China, Europe, and the United States (Thai, Rabaa *et al.*, 2021). Examination of genomics indicated that the nucleotide similarity of the sequences in Vietnam in the two outbreaks was very high (minimum 99.96%, mean 99.97%), combined with familiar mutation exhibiting that virus is not competent to silently infect the community from April 2020 (Phuong, Tung *et al.*, 2021). In Vietnam, each epidemic wave corresponds to the emergence of a new variant with a more robust infectious fitness. During the third wave of epidemics (beginning on January 28, 2021), the outbreak in northern Vietnam occurred rapidly with the main contribution of Alpha variants (Chau, Hong *et al.*, 2021). Then, the fourth wave (beginning on April 27, 2021) had been the worst ever experienced by the

country. In May 2021, all patients in Vietnam were derived by the Delta variant (Nguyen, Wong *et al.*, 2021). In November, this wave had caused 99.9% of total deaths in the country (Hoang, Pham *et al.*, 2022). The Vietnamese government has had to implement unprecedented strict epidemic prevention measures, including encouraging people to isolate themselves at home, mobilizing the participation of the army and military medics, and setting up field hospitals. However, the epidemic situation had been still difficult to control because the Delta variant has high transmissibility.

After November 2021, when the vaccination rate in Vietnam reached a relatively high threshold, government took to restore social life under "new normal" conditions.

The gradual easing of epidemic prevention measures has facilitated the spread of the virus in the community. The first case confirmed that the Omicron variant was recorded in Vietnam on December 19, 2021. Until March 2022, the Omicron became the primary circulating variant and the cause of infections in the Hanoi capital. On March 12, 2022, Vietnam recorded the highest number of infections ever at 454,179 cases/day. This number is much larger than the previous wave of epidemics caused by the Delta variants. Proposes that Omicron will become the dominant variant in Vietnam shortly. Despite the sudden increase in cases, the mortality rate tends to be the opposite.

The number of deaths caused by the Omicron on March 13, 2022, is 95 cases, and the average of the last seven days is 82. These concerns were lower than Delta's 803 cases on September 1, 2021, and the average of the last seven days in 360 cases (according to Vietnam's Ministry of Health). The current research literature indicates that the Omicron variants are more infectious than previously recorded variants (Ren, Wang *et al.*, 2022) (He, Hong *et al.*, 2021). On the other hand, Omicron can cause symptoms less severe (Callaway and Ledford, 2021) (Kupferschmidt and Vogel, 2021) (Ren, Wang *et al.*, 2022). Even so, the high transmission rate of Omicron will pose a significant challenge for diagnostics and vaccine strategies. Therefore, tracking the genetic shifts of these variants is significant. For these reasons, the genetic diversity of the S gene of Omicron variants isolated in Vietnam was investigated. By constructing a network, the genetic relationship of Omicron variants would be revealed, supporting the tracing of a infection source of a new outbreak in the future.

## Materials and methods

*Data collection*

The whole-genome sequences of the Omicron variants were retrieved from the GISAID database. The basic information of all sequences included GISAID's accession numbers, collection date, location, and Pango classification...The sequences of the subvariants of Omicron, BA.3, BA.4, and BA.5 from other regions were also included to data retrieval for further analysis and comparison.

*Multiple sequence alignment (MSA) analysis*

Each individual sequence was aligned with the reference sequence Wuhan-Hu-1 (GenBank accession number: NC_045512.2) using ClustalW. Basing on alignment, for each sequence, S gene was extracted and its nucleotide substitutions was also defined and considered as mutation profile. The whole process from collecting sequences to identification of mutation profile of each sequence was implemented using an in-house developed software.

*Genetic diversity statistic and haplotype network*

Genetic diversity indices and statistical tests such as nucleotide diversity, haplotype diversity, mean of nucleotide difference were calculated using Arlequin 3.5.2.2 (Excoffier and Lischer, 2010).

The haplotype network is also used to determine the genetic relationship of haplotypes in population. A haplotype network exhibits the variation movement of haplotypes in the population. In this study, the Median Joining Network was calculated and visualized with PopART (Leigh and Bryant, 2015).

**Results and discussion**

Genetic diversity analysis showed that Omicron's BA.2 group predominated in Vietnam at 77.67% (Figure 1). Haplotype classification of 1787 S gene sequences has confirmed 362 haplotypes with the haplotype diversity index of 0.9160 ± 0.0037. The mean nucleotide difference between haplotypes was determined to be 20.2873 ± 8.9687. This result indicates the high level of genetic diversity in the Omicron variants in Vietnam and a relative change in the S gene, and the introduction of the new Omicron subvariants.

**Table 1.** Hotspot mutation in the S gene of Omicron (Hotspot mutation >10% according *Alouane et al. (2020)* (Alouane, Laamarti *et al*., 2020).

| Mutation | Amino acid change | Frequency |
|---|---|---|
| C21618T | T19I | 77.73% |
| Del21633-41 TACCCCTGC | Del L24 P24 P26 - A27S | 77.73% |
| C21762T | A67V | 21.71% |
| Del21765-70 TACATG | Del HV69-70 | 21.71% |
| C21846T | T95I | 21.94% |
| G21987A | G142D | 99.50% |
| Del21988-96 TGTTTATTA | Del VYY143-45 | 21.94 – 22.05% |
| DelA22194-96 ATT | NL211I | 17.05% |
| T22200G | V213G | 82.88% |
| Ins22204 GAGCCAGAA | Ins214EPE | 17.01% |
| G22578A | G339D | 99.89% |
| G22599A | R346K | 14.44% |
| C22674T | S371F | 99.78% |
| T22679C | S373P | 99.78% |
| C22686T | S375F | 99.72% |
| A22688G | T376A | 84.56% |
| G22775A | D405N | 81.76% |
| A22786C | R408S | 81.76% |
| G22813T | K417N | 99.72% |
| T22882G | N440K | 54.62% |
| G22898A | G446S | 28.65% |
| T22917G | L452R | 22.89% |
| G22992A | S477N | 77.00% |
| C22995A | T478K | 99.94% |
| A23013C | E484A | 77.06% |
| G23016T | G485V | 22.83% |
| A23040G | Q493R | 76.55% |
| G23048A | G496S | 29.00% |
| A23055G | Q498R | 77.06% |
| A23063T | N501Y | 77.00% |
| T23075C | Y505H | 77.06% |
| C23202A | T547K | 22.66% |
| A23403G | D614G | 100.00% |
| C23525T | H655Y | 98.60% |
| T23599G | N679K | 99.89% |
| C23604A | P681H | 99.89% |
| C23854A | N764K | 100.00% |
| G23948T | D796Y | 100.00% |
| C24130A | N856K | 22.44% |
| A24424T | Q954H | 99.94% |
| T24469A | N969K | 100.00% |
| C24503T | L981F | 22.33% |
| C25000T | None | 100.00% |

The nucleotide composition of the S gene of Omicron indicates the low level of G+C proportion while A+T is the highest, respectfully approximately 37% and 63%.

The analysis of nucleotide diversity confirmed the nucleotide diversity index at 0.0053 ± 0.0026 and recorded 318 polymorphic sites with 275 substitutions. In addition, transitions were the highest, followed by transversions and indel nucleotides, respectively 57%, 29%, and 14%. Especially, our results indicate a high rate of nucleotide C to T conversion and nucleotide deletions, 29.05%, and 12.84%, respectively (Figure 2). We also noted a meager rate of C to G nucleotide changes. Calculating the number of mutations on the S gene shows that the Omicron variants in Vietnam

have an average number of mutations of 40 ± 9 (range 31-69 mutations). Our evaluation of the distribution of mutations in the S gene revealed that the high-prevalence mutations were mainly expressed in the NTD and RBD regions (Figure 3). The missense mutations with a high rate appear mainly in the RBD region. On the other hand, deletion and insertion mutations appear in the NTD region. In particular, we recorded a conserved scene of mutations in the S gene of Omicron variants recorded in Vietnam with a high rate of C21618T G21987A T22200G G22578A C22674T T22679C C22686T A22688G G22775A A22786C G22813T T22882G G22992A C22995A A23013C A23040G A23055G A23063T T23075C A23403G C23525T T23599G C23604A C23854A G23948T A24424T T24469A C25000T (Table 1).

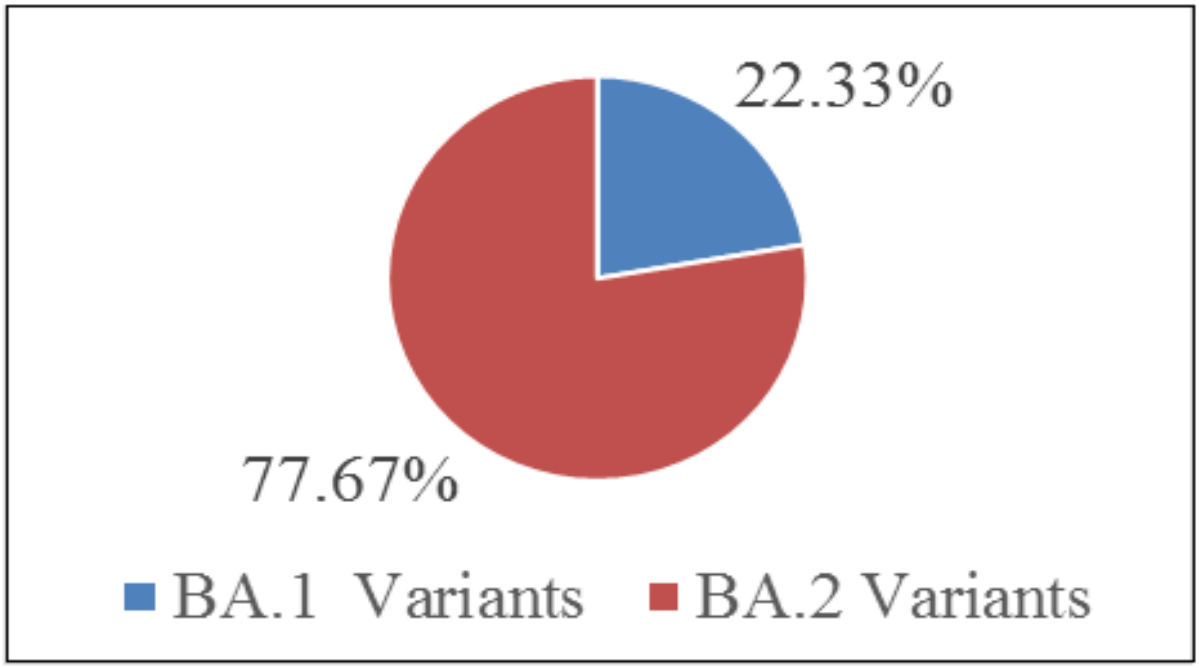


**Fig. 1.** The composition of Omicron variants in Vietnam.

The genetic networks were constructed to examine the drive mutations in the S gene of Omicron. The network exhibited that the first haplotypes of Omicron from December 2021 to January 2022 had a couple of mutations in the S gene, which may be occurred during community transmission of the virus because the haplotypes are closely related, differing only by 1 to 2 nucleotides (Figure 4). By March 2022, we recorded haplotypes had entered Vietnam when numerous mutations were introduced in the S gene (from 5 to 7 nucleotides) of these haplotypes that appeared in February compared to the previous haplotypes.

However, the changing haplotypes in March-April mainly originate from the first dominant haplotypes. The rest of the following haplotypes are almost restricted. In analyzing the genetic diversity of the S gene of Omicron, we recorded high genetic diversity in Vietnam. In which 362 haplotypes were identified with high haplotype diversity, and the average nucleotide difference between haplotypes existed at 20 nucleotides. Mutation analysis results showed that the average number of mutations in the S gene existed 40 ± 9 (range 31 to 69). Meanwhile, the study of Colson *et al.* (2022) (Colson, Delerce *et al.*, 2022) revealed the number of mutations in the whole genome of Omicron at 65.9 ± 2.5. Our results indicated the number of mutations in the S gene accounts for a relative proportion of the total number of mutations in the genome (Singh and Yi, 2021) (Chaw, Tai *et al.*, 2020). Our observations are also consistent with previous studies showing that the S gene of SARS-CoV-2 has the most significant number of mutations in the genome to help enhance host receptor compatibility (Wei, Shan *et al.*, 2021).

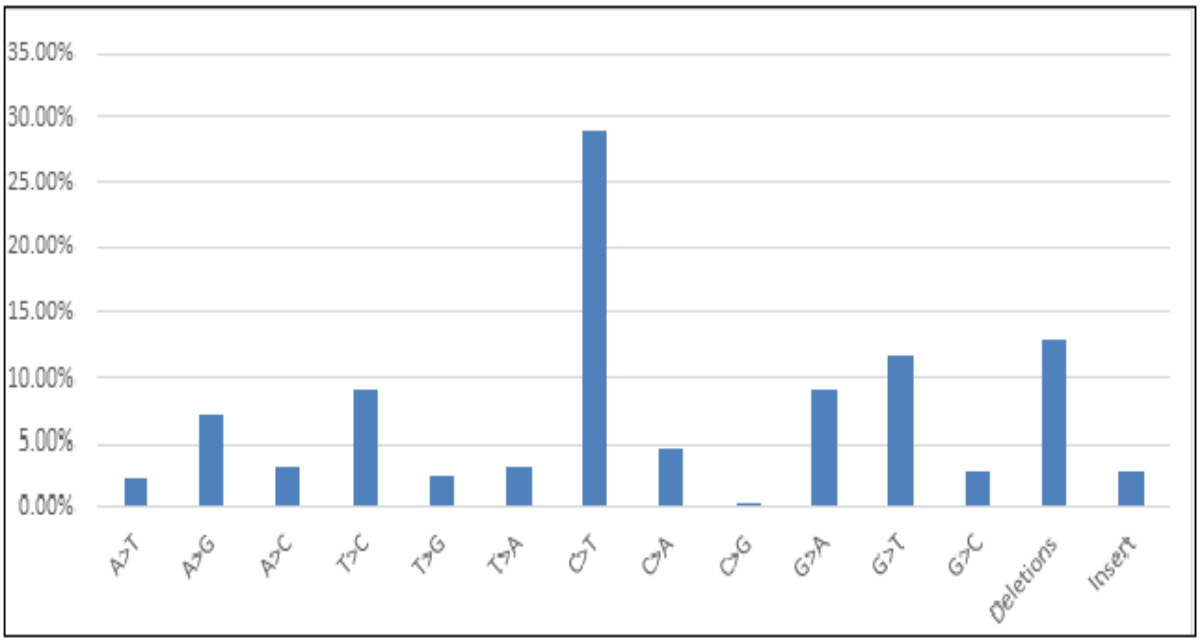


**Fig. 2.** Frequency of nucleotide changes.

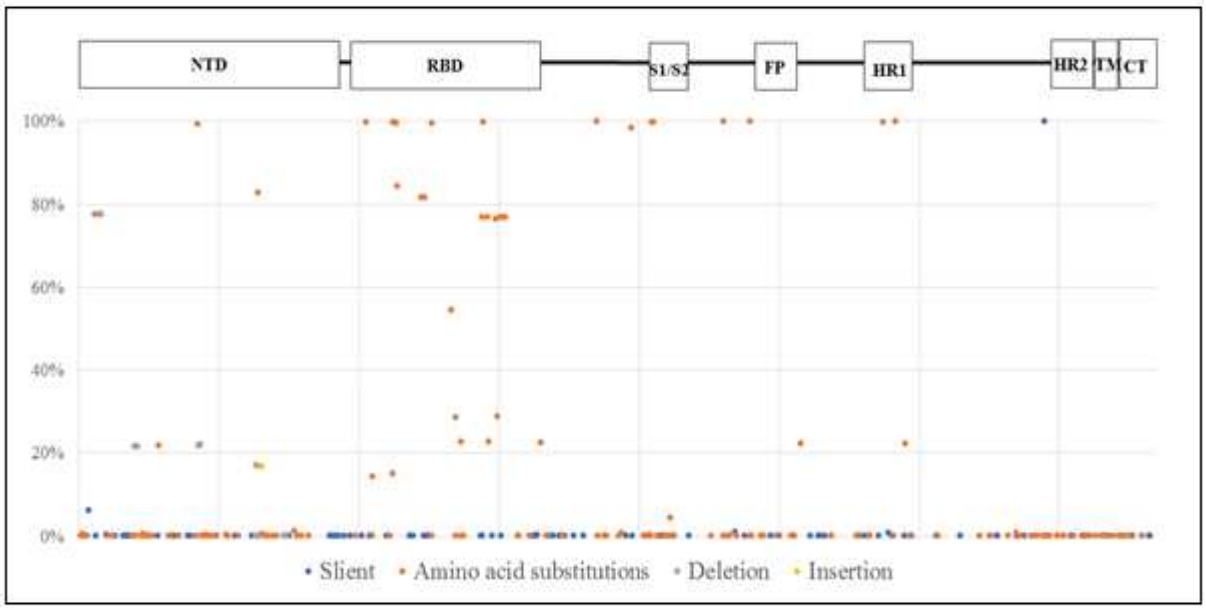


**Fig. 3.** The distribution of mutations in the S gene of Omicron.

The analysis of nucleotide polymorphism displayed that a high level of missenses mutation appeared in the RBD region, and deletion mutations were most assumably to occur in the NTD. In the NTD region, deletion mutations have been shown to neutralize antibodies and reduce vaccine protection. In particular, this region of Omicron recorded insertion of 9 nucleotides (GAGCCAGAA) at position 22204, thereby forming an EPE loop on the spike protein (Ni, Lau *et al.*, 2021). Proposals suggest that this EPE loop is likely to worsen the neutralization of antibodies. In addition, missense mutations (G22578A (G339D), C22674T (S371F), T22679C (S373P), C22686T (S375F), C22995A (T478K)) in the RBD region stand conserved when it introduces the high rate. Previous publications have shown that these amino acid substitutions in RBD enable Omicron to escape neutralizing antibodies or increase the spike protein's binding efficiency to the hACE2 receptor (Di Giacomo, Mercatelli *et al.*, 2021) (He, Hong *et al.*, 2021). In addition, the furin cleavage site (FCS) also recorded highly conserved mutations, namely

A23403G (D614G), C23525T (H655Y), T23599G (N679K), C23604A (P681H). The shared characteristic of these mutants is to enhance the efficiency of spike protein cleavage to activate the binding of the protein to the hACE2 receptor during viral infection into host cells (He, Hong *et al.*, 2021). Indeed, amino acid substitutions in the FCS region almost changed the mechanical morphology of the cleavage site, thereby changing the infectivity of Omicron (Abbas, Kusakin *et al.*, 2022).

The genetic network of the S gene of Omicron in Vietnam may authenticate a relative correlation between infection and mutation. We found that the sources of infection of Omicron in Vietnam arise from early variants. The outbreak was in December 2021, and there were novel mutations in the S gene that lasted until January 2022. After that, the Vietnamese government gradually took steps to loosen COVID-19 prevention measures and create "new normal" conditions in society. This action is an opportunity to introduce new variants of Omicron into Vietnam and prevent rapid infection in the community. The situation was recorded until March 2022, and the Omicron variants caused most of the infections recorded in the Hanoi capital. Coincides with the change in the genetic network of Omicron (Figure 4), the haplotypes appearing in February have numerous nucleotide differences from the haplotypes appearing earlier in Vietnam, demonstrating the new variant migration of these genes. Since then, the haplotypes that appeared in March-April accounted for the majority and had involved shifts in the S gene through community transmission.

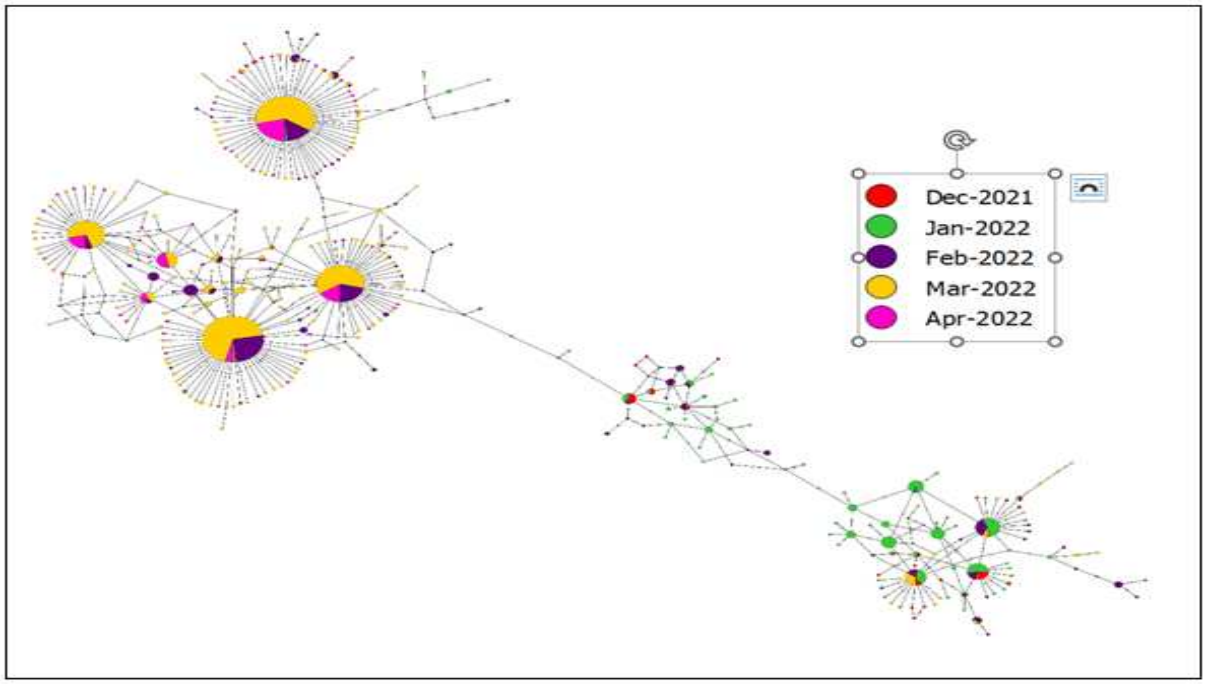


**Fig. 4.** Median Joining Network of the S gene of Omicron in Vietnam.

In order to determine the cause of the intense outbreak of Omicron in Vietnam in March-April, we analyzed the genetic network of Omicron by the variants group. The results reveal that during this period, the dominative prevalence of the BA.2 (Figure 5). Recent studies show that BA.2 is more infectious than BA.1 because of its ability to "stealth" against neutralizing antibodies. Thereby consistent with the popularity of Omicron in Vietnam when BA.1 appeared first, but the haplotypes are primarily undersized in number, and the nucleotide change in the S gene were occasional. Meanwhile, cluster BA.2 dominates the number and modifications in the S gene.

This shows the correlation between the genetic diversity variation on the S gene and the effectiveness of transmission fitness.

Recently, the predominance of two subvariants, BA.4 and BA.5, is causing significant outbreaks in the US in early June 2022. Furthermore, these two variants have rapidly replaced the BA.2 in Africa in April 2022 (Tegally, Moir *et al.*, 2022). Current recommendations suggest that BA.4 and BA.5 share common Omicron mutations and are closely related to BA.2 (Tegally, Moir *et al.*, 2022) but were dominant when these variants had transmission rate that was about 36% higher than BA.2 (Mohapatra, Kandi *et al.*, 2022). Therefore, through the genetic network, we consider the relationship between BA.4 and BA.5 appearing in the world with BA.2 in Vietnam. Our results determine the closeness relationship of BA.4 and BA.5 to cluster BA.2 appearing in Vietnam (Figure 5). In particular, the haplotype of BA.2 in Vietnam has the closest relationship with clusters BA.4 and BA.5, with only two nucleotide differences, T22917G (L452R) and T23018G (F486V). Among them, the most notable is the L452R mutation, which is one of the primary mutations that increase the transmissibility of Delta (Motozono, Toyoda *et al.*, 2021) (Goher, Ali *et al.*, 2021) – the variants that caused the worst outbreak ever worldwide.

The F486V mutation located in the hACE2 receptor-interacting region (Lan, Ge *et al.*, 2020) appears to be potentially associated with increased transmissibility of BA.4 and B.5 compared to BA.2. Clearly, we necessary focus on novel mutations in the S gene of BA.4, BA.5 and new variants in the future.

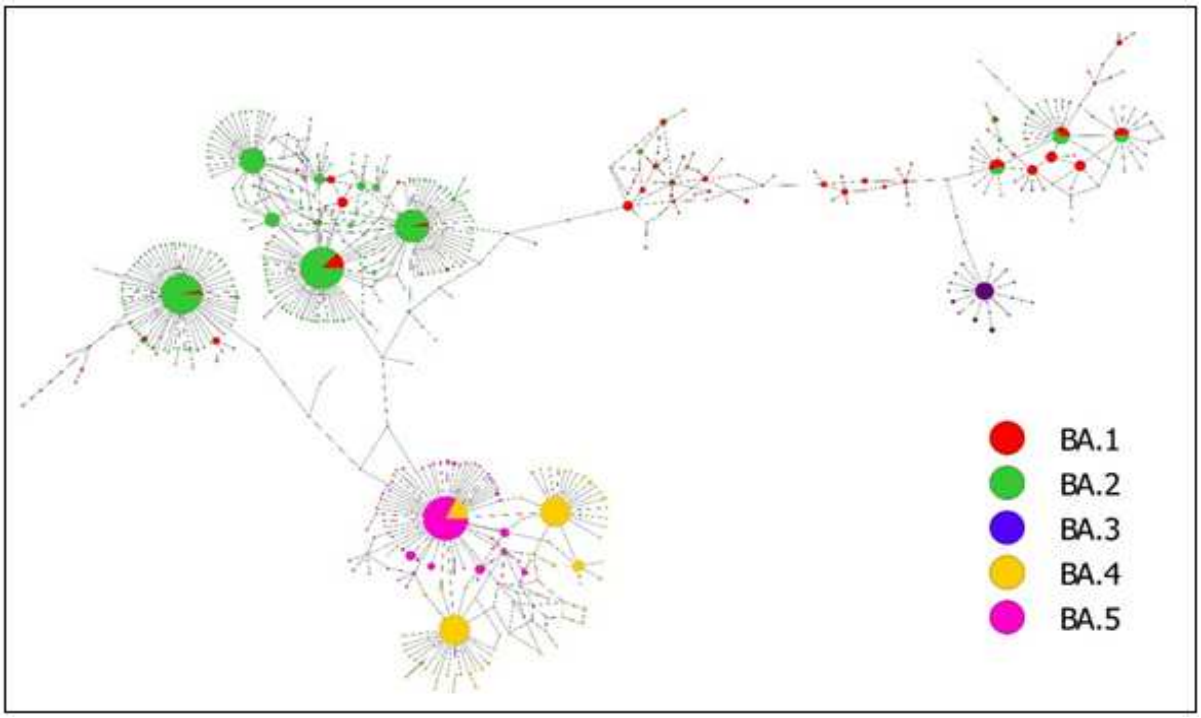


**Fig. 5.** The S gene' Median Joining Network of Omicron in Vietnam and other Omicron variants worldwide.

In summary, this study exhibits that the S gene region of the Omicron strain in Vietnam has high genetic diversity and numerous mutations. Through the genetic network, we provide additional information on the correlation of mutations in the S gene with infectivity and the relationship of Omicron variants. From there, it authenticates that tracking mutations appearing on the S gene provides essential information in the infection course and new positive fitness of SARS-CoV-2.

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