Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Short Communication

Genomic profiles of vaccine breakthrough SARS-CoV-2 strains from Odisha, India

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In India, five COVID-19 vaccines are authorized for emergency use, of which the adenovirus-vector based vaccine from Oxford University and AstraZeneca UK, marketed as COVISHIELD, and the indigenous inactivated virus vaccine COVAXIN by Bharat Biotech are majorly deployed through government and private healthcare centers. Both the vaccines pose tolerable safety outcomes and enhanced immune responses (Ella et al., 2021; Voysey et al., 2021). Recent *in vitro* studies showed that sera from the Pfizer- or the AstraZeneca-vaccinated individuals are less effective in neutralizing the Delta variant compared with the Alpha (B.1.1.7) variant (Planas et al., 2021). In this study, we summarize 36 COVID-19 vaccine breakthrough cases, which were SARS-CoV-2 reverse transcription polymerase chain reaction positive despite evidence of antibody response following vaccination.

The isolated ribonucleic acid was subjected to real-time quantitative polymerase chain reaction, and samples with cycle threshold values <35 (ORF1ab and N gene) were considered for the study. Sequencing libraries were prepared with COVIDSeq kit and sequenced using NextSeq-550 platform (Illumina). Non-host (human) reads extracted using Kraken2 taxonomic classifier (Wood et al., 2019) were aligned using BWA against the Wuhan-Hu-1 (NC_045512.2) reference genome. Single nucleotide variants and short insertion deletion mutations were called using GATK4 Haplotypecaller. Consensus sequences generated using BCFtools consensus and regions having no aligned reads were hard masked. Rooted (root: NC_045512.2) phylogenetic tree of 549 sequences (512 unvaccinated sequences in the same timeframe from Odisha) was constructed using the method described in the study by Raghav et al. (2020).

As a part of the regular COVID-19 genomic surveillance, we identified and sequenced 36 vaccine breakthrough infection cases. The study group consisted of 12 women and 24 men with age ranging from 23 to 65 years (median = 38.50, SD = 13.58). All subjects except two were fully immunized with two doses of either COVAXIN/BBV1552 (n = 8) or AZD1222/ COVISHIELD (n = 26). The interval between two vaccine doses ranged from 27 to 49 days, with a median interval of 35 days (n = 34), and the onset of infection ranged from 6 to 98 days after vaccination (median = 74, SD = 25, n = 31). Of the 36 cases, 33 reported either single or a combination of common COVID-19–related symptoms, i.e., fever, body pain, sore throat; one individual did not report any symptoms during sample collection, and for the other two samples, the symptoms were not reported. The specimens were collected between March 29 and June 15, 2021.

In the study group, 19.44% patients reported comorbidities, i.e., diabetes and blood pressure; the remaining 72.22% patients did not report any complications, and disease history is not reported

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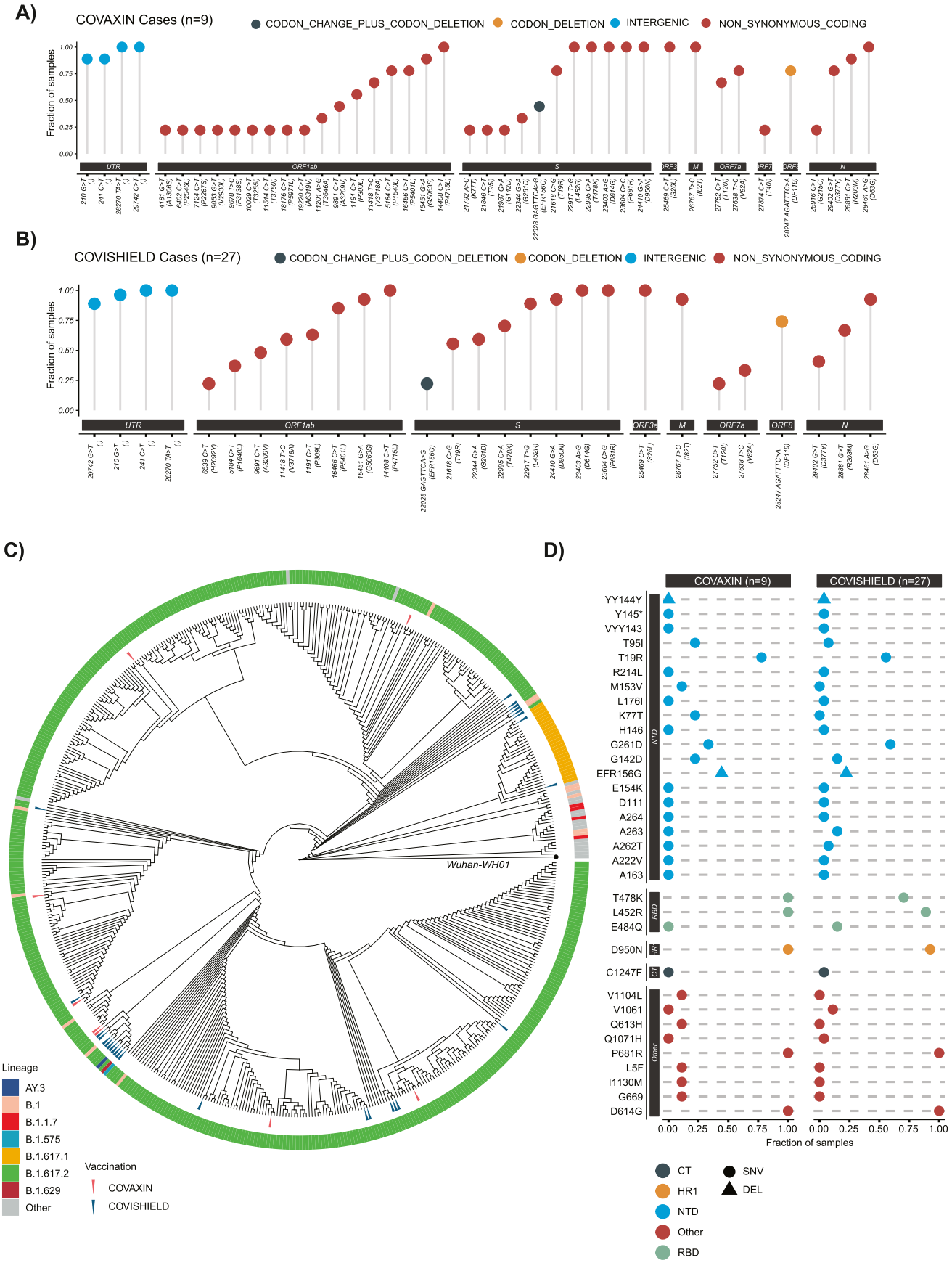

Figure 1. SARS-CoV-2 variants of concern and phylogenetic analysis of vaccine breakthrough cases; (A & B) Genome-wide nonsynonymous mutations present in high fraction (>20%) of samples, grouped by the vaccines, (C) Phylogenetic tree (n = 549) of our study genomes along with SARS-CoV-2 sequences prevalent during the same time frame from Odisha, the tree is rooted with the Wuhan-Hu-01 assembly, and (D) Nonsynonymous mutations observed in different domains of spike protein grouped by vaccination type.

for three cases. Of 36 patients, only one patient was hospitalized with comorbidities, and 27 recovered in home isolation; for eight individuals, the treatment status is not reported. Except for three unknown cases, the rest of the patients did not report any prior history of SARS-CoV-2 infection at the time of sample collection.

Of the 36 cases, 29 were identified as the variant of concern Delta (80%), two classified as Kappa (B.1.617.1) (~6%), two as B.1 (~6%), and one each in Delta (AY.3), B.1.575, and B.1.629 lineages. In COVAXIN breakthrough cases, 9/9 classified as the Delta variant; for COVISHIELD, 20/27 were classified as Delta, 2/27 as Kappa, 2/27 as B.1, 1/27 as AY.3, 1/27 as B.1.575, and 1/27 as B.1.629. When we looked for high frequency variants (present in >20% of samples) in these two vaccination groups, COVAXIN cases contained an overall higher number of variants (n=42) than the COVISHIELD group (n=28) (Figure 1 A, 1B). Although two of the cases were classified as B.1, we found that both of them were classified as 21A (Delta) by Nextclade, having S:D614G and S:P681R mutations along with other lineages. We also found strong phylogenetic closeness of these B.1 lineages with the Delta (B.1.617.2) variant cases collected in the same time frame (Figure 1C). Looking into spike domain–specific mutations, we observed an emergence of EFR156G substitution (delE156, delF157, and R158G) in N-terminus domain, which is becoming a common trait of recently reported Delta (B.1.617.2) variants (Liu et al., 2021). Interestingly, most of the breakthrough cases shared the presence of S:L452R and S:T478K in receptor-binding domain along with S:D614G and S:P681R near the S1-S2 furin cleavage site. All these spike variants have been proposed to be associated with increased infectivity through different mechanisms (Figure 1D) (Harvey et al., 2021).

In this study, we found that the SARS-CoV-2 variant of concern Delta (B.1.617.2) is overrepresented in the vaccine breakthrough cases, which could be because of its higher prevalence as well during that period. Recent studies suggested that the effectiveness of BNT162b2 (Pfizer) and ChAdOx1 (AstraZeneca) has been reduced in comparison with the Alpha (B.1.1.7) variants. In addition, the same has been observed in the neutralization capability of sera from fully vaccinated individuals (Lopez Bernal et al., 2021; Planas et al., 2021). One other *in vitro* study suggested that S:L452R and S:E484Q present in the RDB domain of spike protein are responsible for immune escape and thereby a 3- to 6-fold decrease in the neutralization capability of BNT162b2 sera (Ferreira et al., 2021).

Along with global reports of emerging variants of concerns and vaccine breakthrough infection cases, there are new threats emerging in India as well. The presence of three new Delta (AY.1, AY.2, and AY.3) sublineages has been observed in parallel with the Delta (B.1.617.2) variant that was first observed in India. Recent reports of breakthrough infection cases from India have also pointed out the predominance of Kappa (B.1.617.1) and Delta (B.1.617.2) variants (Singh et al., 2021). Continuing the virus genomic surveillance is necessary for devising new and improved interventions for COVID-19.

Disclosures

The authors report no competing interests.

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Institutional Review Board approval

The study plan was approved by the Institute of Life Sciences Institutional Biosafety Committee (Ref no. V-122-MISC/2007-08/01) and the Institutional Human Ethical Committee (Ref no. 109/HEC/21). All necessary patient/participant consents have been obtained, and the appropriate institutional forms have been archived.

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