Antibody evasion and receptor binding of SARS-CoV-2 variants PQ.16.1.1 and RK.1

Since its rapid global spread beginning in late 2024, the SARS-CoV-2 variant NB.1.8.1 has progressively displaced older omicron variants, and has established near-total dominance in Asia.[1–3] More recently, two NB.1.8.1-derived sublineages, PQ.16.1.1 and RK.1, have emerged and expanded substantially, particularly in China and Singapore (appendix p 7). Specifically, the sublineage PQ.16.1.1 acquired the amino acid substitutions Asp253Gly (within the *N*-terminal domain), alongside Asn417Thr, Asp420Asn, and Ile478Thr (within the receptor-binding domain) relative to the parental NB.1.8.1 strain (appendix p 8). Concurrently, the RK.1 sublineage (formally classified as a descendant of the PQ.17.7.2.1 branch) acquired Asp420Asn, His445Pro, and Ile478Thr (appendix p 4). Furthermore, PQ.16.1.1 has continued to evolve into the SV series sublineages (predominantly SV.2 and SV.2.1), which have maintained all receptor-binding domain mutations, including Asp420Asn, and have subsequently come to dominate the circulating SARS-CoV-2 strains in Singapore (appendix p 7).

PQ.16.1.1 and RK.1 share two mutations: Asp420Asn and Ile478Thr. However, because the Ile478Thr reversion mutation also appears in several non-dominant progeny of the NB.1.8.1 lineage, Asp420Asn is likely the primary driver of their transmission advantage. The independent, convergent acquisition of Asp420Asn, a mutation that previously predicted to cause immune evasion of class 1 neutralising antibodies,[4–8] across distinct evolutionary branches of the NB.1.8.1 family tree strongly indicates powerful, population-level positive selection. Global genomic surveillance data (appendix p 1) collected between March 1, and July 10, 2026, with sequences submitted to the Global Initiative on Sharing All Influenza Data and the National Center for Biotechnology Information virus databases, showed that Asp420Asn-carrying NB.1.8.1 sublineages have reached regional dominance across the Asia–Pacific region and are progressively displacing other circulating mutations (appendix p 7). Here, we investigated the receptor engagement and humoral evasion characteristics of these variants carrying the Asp420Asn variants.

We first assessed the human angiotensin-converting enzyme 2 (hACE2) receptor engagement of NB.1.8.1 and PQ.16.1.1. Surface plasmon resonance showed that the recombinant PQ.16.1.1 receptor-binding domain exhibited a significantly lower binding affinity for hACE2 than NB.1.8.1, as reflected by an increased equilibrium dissociation constant (appendix pp 5, 9–10). Previous studies have extensively investigated the effects of the Asn417Thr and Ile478Thr substitutions on hACE2 binding and shown that these substitutions do not substantially impair binding.[4–8] Therefore, the reduced hACE2-binding affinity of PQ.16.1.1 should be attributable predominantly to the Asp420Asn substitution. Notably, the affinity of the PQ.16.1.1 receptor-binding domain for hACE2 remains stronger than that of the XFG variant. Next, we generated vesicular stomatitis virus pseudotypes bearing the spike proteins of these variants and measured their susceptibility to soluble hACE2-mediated inhibition, an assay that measures the receptor-binding strength and engagement efficiency of the variant's spike glycoprotein. Consistently, both PQ.16.1.1 and RK.1 showed significantly reduced spike-mediated hACE2 engagement relative to NB.1.8.1, but their engagement efficiency remained similar to or stronger than that of XFG (appendix p 11). Collectively, these results suggest Asp420Asn reduces receptor engagement efficiency; however, engagement efficiency remains within the range required for effective viral prevalence.

Next, we evaluated humoral immune evasion by use of human convalescent plasma and a panel of receptor-binding domain-targeting neutralising monoclonal antibodies (mAbs). The individual plasmas were collected between April 9, and Aug 26, 2025 in Beijing, China, when NB.1.8.1 was dominant (appendix p 6). Compared with NB.1.8.1, both PQ.16.1.1 and RK.1 exhibited significantly lower neutralisation titres against Wuhan-Hu-1-primed plasma (from individuals who received Wuhan-Hu-1 inactivated vaccines). By contrast, susceptibility to omicron-primed plasma (from unvaccinated individuals whose first exposure was to an omicron variant) remained not significant. These results highlight that the Asp420Asn mutation might specifically exploit vulnerabilities in the antibody response induced by Wuhan-Hu-1 priming (appendix p 12).

mAb profiling revealed that both PQ.16.1.1 and RK.1 substantially resisted class 1 antibodies, with RK.1 showing a more extensive loss of neutralisation (appendix p 13). This result aligns with predictive models identifying residue 420 as an immune-pressure hotspot within the class 1 epitope, which physically overlaps the hACE2-binding footprint.[4–8] Combined with the reduced hACE2 engagement efficiency of RK.1 compared with PQ.16.1.1, this result also indicates that 417Asn (present in RK.1) exhibits stronger class 1 antibody evasion compared with 417Thr (present in PQ.16.1.1) at the cost of hACE2 binding strength, given that residue 417 is their primary mutational difference on the receptor-binding domain.

Compared with class 1 mAbs, PQ.16.1.1 and RK.1 showed little to no antibody evasion against

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class 3 and class 1/4 mAbs. The elicitation of these omicron-specific antibody classes varies sharply across populations and dominates the antibody response in individuals who were previously infected with omicron variants.[6–8] This observation aligns with the fact that PQ.16.1.1 and RK.1 did not cause as substantial immune evasion in individuals who were previously infected with omicron variants as in unvaccinated individuals who received Wuhan-Hu-1 inactivated vaccines (appendix p 12).

In summary, the convergent acquisition of the Asp420Asn substitution in NB.1.8.1 sublineages again illustrates a classic SARS-CoV-2 receptor-binding domain evolution trade-off: a sacrifice in hACE2 receptor engagement in exchange for profound, targeted evasion of class 1 neutralising antibodies. This phenomenon has been frequently observed in the evolutionary trends of SARS-CoV-2 omicron variants, as shown recently by the evolution of JN.1 sublineages.[9–10] Interestingly, the Asp420Asn mutation did not occur in the XFG backbone. XFG's hACE2 binding is far weaker than that of NB.1.8.1, meaning that XFG does not have the buffering room necessary for the evolution of 420Asn. Given the increased evasion of class 1 antibodies by these Asp420Asn-carrying sublineages, these variants will likely spread from Asia and begin to prevail in countries where mRNA vaccination is common and populations are enriched with class 1 neutralising antibodies. This underscores the need for continued, stringent global surveillance of those SARS-CoV-2 variants, especially for future compensatory mutations that could restore receptor engagement while preserving this newly acquired immune evasion mutation.

YC has provisional patent applications for the BD series antibodies (WO2024131775A9 and WO2023151312A1) and is the founder of Singlomics Biopharmaceuticals. All other authors declare no competing interests.

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