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EDITORIAL COMMENTARY

Uncovering Ways That Emerging Severe Acute Respiratory Syndrome Coronavirus 2 Lineages May Increase Transmissibility

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(See the Brief Report by Kidd et al, on pages 1666–70.)

With the emergence of novel lineages that increase transmissibility and reduce the efficacy of vaccines, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic is entering a new and dangerous phase. One of the first lineages of concern recognized was B.1.1.7 (also known as VOC-202012/01 and 501Y.V1), initially reported in the United Kingdom (UK) in September 2020. B.1.1.7 has risen quickly in prevalence across multiple independent regions [1] and appears to be approximately 50% more transmissible than most other SARS-CoV-2 genotypes [2–4], a finding that has prompted intensified lockdown measures within the UK and travel restrictions in many countries. Preliminary evidence suggests that current vaccines and neutralizing antibodies remain similarly effective against B.1.1.7, in contrast to B.1.351 and P.1, where their effects appear partially attenuated [6–8].

B.1.1.7 contains 17 mutations that affect the amino acid sequence of SARS-CoV-2 proteins, including 14 single amino acid mutations and 3 deletions [1]. One of these mutations results in a deletion of amino acids 69 and 70 in the Spike (S) protein. Although not believed to be the cause of increased transmissibility, this deletion interferes with the primer/probe binding for the S gene target in the Thermo taqpath assay, termed S gene target failure (SGTF). Thus, SGTF can be used as a proxy for B.1.1.7 lineage if the prevalence of B.1.1.7 is high (other lineages also contain S:69–70 deletions and may cause SGTF). This represents a fortuitous coincidence and an efficient way to monitor and study the B.1.1.7 variant because whole-genome sequencing is a far more laborious and slow process. In this issue of *The Journal of Infectious Diseases*, Kidd et al, working as a part of the NHS Lighthouse network, investigated potential differences in viral shedding between variants circulating in the UK, with SGTF as a proxy for B.1.1.7 viruses. The authors found that viruses with SGTF had a lower cycle threshold (Ct) on quantitative real-time polymerase chain reaction (PCR). Cycle threshold is inversely correlated with viral load, so this indicates that patients with SGTF have a higher nasopharyngeal viral load than patients with non-SGTF viruses. Given the high prevalence of B.1.1.7 at the time of sampling, they attribute this effect to B.1.1.7.

What are the implications of this finding? A higher viral load in B.1.1.7 patients could provide a mechanism for the increased transmissibility of B.1.1.7. However, a major limitation of the current study is that the proportion of non-B.1.1.7 lineages with SGTF in their sample is unknown because viral sequencing was not performed, and there are non-B.1.1.7 variants that also have SGTF. The authors cite data suggesting that B.1.1.7 was highly prevalent at the time and place of their sampling (comprising approximately 80% of the SGTFs) and, therefore, argue that SGTF is an effective marker for B.1.1.7 in their study sample. Indeed, the fact that a subset of the SGTF group is made up of non-B.1.1.7 variants makes the observed Ct differences between the SGTF and non-SGTF groups even more impressive. During PCR, there is an approximate doubling of template material during each cycle, so a difference of 1 Ct approximately corresponds to a 2-fold difference in starting material. The median Ct difference between the SGTF and non-SGTF samples was approximately 4 Cts, representing approximately 16-fold higher viral shedding in the SGTF cases. This is a large difference that could certainly have consequences for the risk of transmission or disease severity. Viral load has been associated with adverse outcomes in multiple studies [9–11], although a causal link is not established.

The published experiments appear technically sound and demonstrate a consistent, strong effect that is biologically plausible. The authors have excluded several potential technical artifacts related to PCR while acknowledging that

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their findings are preliminary and must be repeated by other investigators before the evidence is definitive. The single-site, case-control design carried out in a single laboratory could be affected by unmeasured technical and epidemiological confounding, including the timing between infection and testing. These limitations are understandable given the circumstances, and the authors should be commended for publishing critical data in close to real time during a pandemic. Future studies should expand on the work of Kidd et al by analyzing longitudinal data from individual patients and conduct hypothesis-directed experimental studies in animal models.

If the association between B.1.1.7 and increased viral load is substantiated by other studies, a related question is which of the mutations in B.1.1.7 is responsible for this effect. Much speculation has centered around the Spike N501Y substitution, which increases affinity of a critical site at the binding site between Spike and the human ACE2 receptor [12], and it appears to have occurred via convergent evolution in multiple emerging lineages (including B.1.351 and P.1). However, it is important not to jump to conclusions and to study the individual mutations individually and in combination. The patterns of recurrent mutations, especially involving the triad of Spike mutations N501Y, E484K, and K417 found in B.1.351 and P.1, suggest that these mutations may not be statistically or functionally independent.

The emergence of B.1.1.7 and its associated mutations is reminiscent of the earlier studies of lineages that emerged in January 2020 and contain an aspartic acid to glycine substitution at position 614 of Spike (D614G) [13, 14]. Several studies showed that D614G may be associated with a higher nasopharyngeal SARS-CoV-2 viral load [13, 15, 16], but the effect is much smaller (1–3 Cts) compared to that which Kidd et al observed for SGTF. If the mechanism of transmissibility in both cases is increased viral load, then the B.1.1.7 lineage may have a larger impact on SARS-CoV-2 epidemiology than D614G.

The work of Kidd et al is a critical first step in understanding the unique phenotypic properties of the B.1.1.7 lineage and their consequences for the ongoing pandemic. This report also serves as a testament to the quality of the UK's genomic surveillance system and connected laboratory network, which is a model for the rest of the world. As viral evolution continues to shape the SARS-CoV-2 pandemic in profound and concerning ways, there is an urgent need to increase the scope and speed of genomic surveillance and to understand the phenotypic properties of emerging viral genetic variation.

While we await additional studies on the relationship of emerging lineages and viral phenotypes, clinicians, scientists, public health officials, and policy makers should begin to consider the consequences of viral lineages with evolving phenotypes. Variants with increased transmissibility reinforce the importance of continued public health vigilance and infection prevention measures. Furthermore, the emergence of these variants in multiple parts of the world highlights the need for universal vaccine accessibility, including in developing regions, because uncontrolled infection anywhere constitutes a potential risk to vaccine efficacy everywhere.

Notes

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