Is SARS-CoV-2 Variant (B.1.617) is going to be a Global Variant of Concern?

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Abstract

The B.1.617 variant, which is widely considered to be one of the primary reasons behind the huge surge in number of infections across India during the second wave of the pandemic, has been termed as a 'global variant of concern' by WHO. It has already spread to more than 40 countries and several countries have put travel restrictions for passengers coming from India as a result of the surge in cases here. The B.1.617 variant with increased transmissibility is likely to affect more children in the form of third wave that is going to be a greatest concern across the world.

Though the variant, which has two mutations — E484Q and L452R — in its spike protein, is believed to be driving the Covid surge in India, there is still no definitive evidence to conclude if it is deadlier or is causing a more severe form of infection. One reason why more children may be getting affected is because the B.1.617 variant has a mutation that makes it easier for the virus to latch onto human cells and cause an infection. Lab studies have shown that the B.1.617 variant can attach with more strength to the ACE-2 receptors, the site where the corona virus binds to our cells, than the earlier versions of the virus.

Children generally have underdeveloped sinuses and fewer ACE-2 receptors which protect them from getting infected. Angiotensin-converting enzyme 2s,or ACE-2, are the doors that allow SARS-CoV-2 to enter the body. Since children have less ACE-2 in their lungs, they are less likely to be affected. But the B.1.617 variant could have changed that, this variant can possibly attach with more strength to the ACE-2 receptors, which means it can then have less attachment sites and still infect people. This could be one of the reasons why children are more vulnerable to this new variant.

The B.1.617 version of the corona virus carries the ominous nickname "double mutant," but it has more than two sequence changes from older SARS-CoV-2 variants, and little is known so far about the effects of these alterations, if any, on disease severity or the virus's ability to evade immunity gained through infection or vaccines.

B.1.617's double mutant moniker comes from changes it harbors that are similar to those in other known variants. One mutation, known as L452R, is also found in the B.1.427/B.1.429 variant first identified in

California, where it has been associated with increased transmissibility. Another B.1.617 mutation, called E484Q, is similar to the E484K mutation found in the P.1 variant that was first detected in Brazil and the B.1.351 variant, also known as the South African variant. E484K is known as an "escape mutation" because it appears to help the virus partially evade immunity conferred by prior infection or vaccines.

B.1.617 is now the dominant variant in India's hardest-hit state, Maharashtra. In its most recent epidemiological update, released April 27, the World Health Organization (WHO) notes that multiple other variants are also circulating in the country, and that "Preliminary modelling by WHO based on sequences submitted to GISAID suggest that B.1.617 has a higher growth rate than other circulating variants in India, suggesting potential increased transmissibility." It is going to be leading to be a catastrophe leading to third wave and a global variant of concern.

Keywords: Covid-19,SARS-CoV-2, B.1.617, Third Wave, WHO, E484Q, E484K, ACE-2

Introduction

The "Indian variant" of SARS CoV-2, more accurately called B.1.617, is a coronavirus variant that has played a big part in the second wave of infections in India and has spread to many other countries including the UK. There is growing evidence that it spreads faster than the B.1.1.7 variant from the UK, or Kent variant, but this had yet to be definitively established at the time of writing.

There are three notable sub-variants of B.1.617. The one of most concern is called B.1.617.2, which was first detected in India in December 2020. It remained rare until early March, when it became the dominant variant reported. It has spread to many other countries, and is increasing rapidly in some. In the UK, it has become more common than B.1.1.7, though overall case numbers remain low.

What variants of concern have been found?

B.1.1.7 lineage

One new strain with a particularly large number of mutations was first noted in the United Kingdom in September 2020, termed VOC 202012/01 (a variant of concern – December 2020), and is also known as 20B/501Y.V1by the United States Centers for Disease Control and Prevention (CDC). This strain, which has since been termed the B.1.1.7 variant, has a total of 23 mutations with 17 amino acid changes.

Since its identification in Britain, the B.1.1.7 strain has been found in over 90 different countries around the world. In fact, as of April 7, 2021, the B.1.1.7 variant is the most common source of new SARS-CoV-2 infections in the United States.

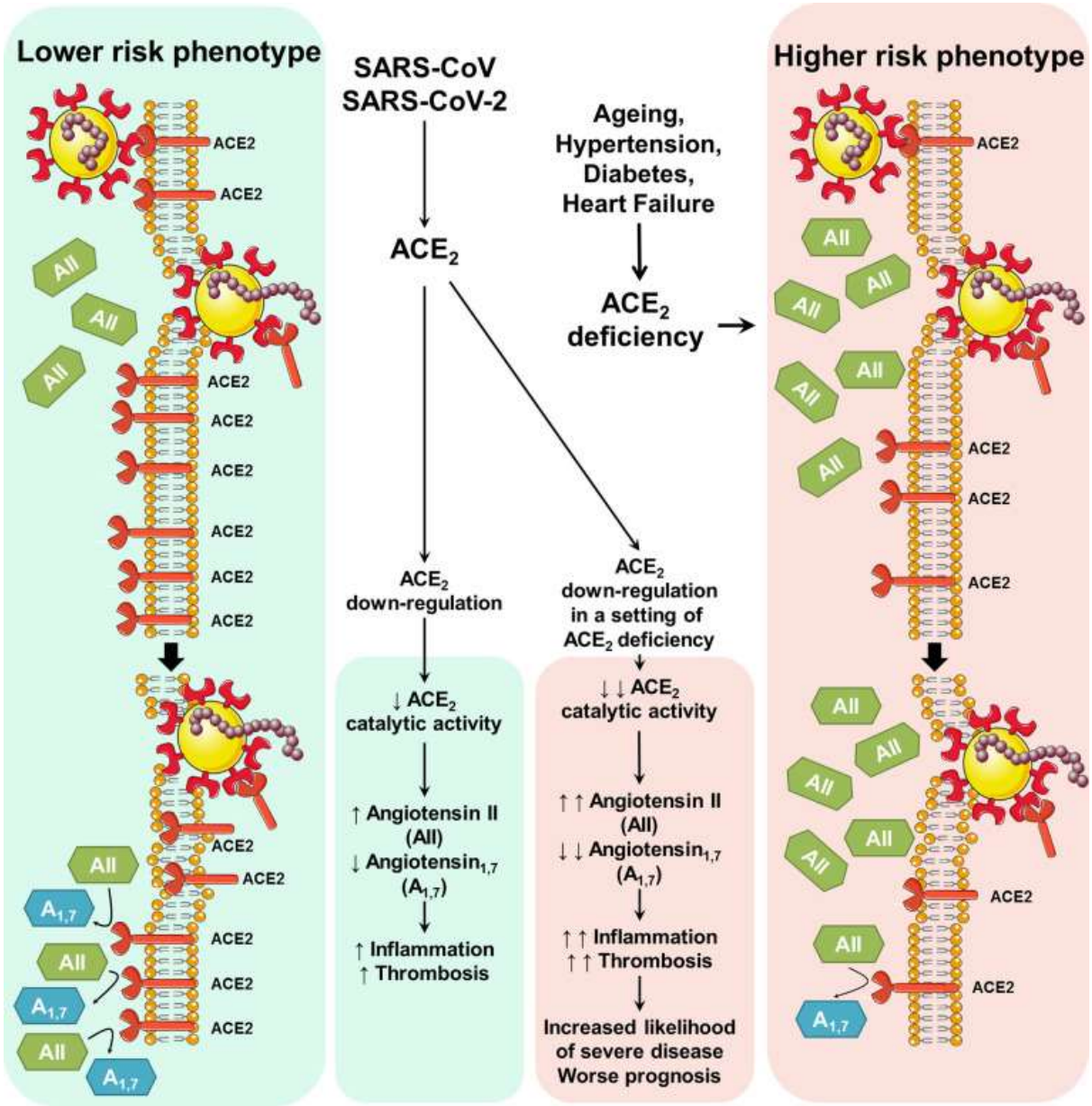
What is concerning about this specific strain is that it is thought to be 30-50% more infectious than the original SARS-CoV-2 strains and may be more deadly. The B.1.1.7 strain has the following key mutations:

- N501Y
- P681H
- H69-V70 and Y144/145 deletions

SARS-CoV-2 interacts with ACE2 receptors in the body using its spike protein. This consists of two subunits, the first of which contains the receptor-binding domain. The B.1.1.7 lineage has a mutation on the receptor-binding domain, specifically with an asparagine amino acid being replaced with tyrosine at position 501, thus the mutation is termed N501Y.

Additionally, the strain often shows a deletion of amino acids 69 and 70, also seen to arise spontaneously in other strains, causing a conformational change of the spike protein.

At position 681, a mutation from a proline amino acid to histidine has also been found to arise spontaneously in several strains and is prominent in B.1.1.7, as is a mutation to open reading frame 8, the function of which is not yet fully understood.



Potential impact of ACE2 down-regulation induced by viral entry in a setting of pre-existing ACE2 deficiency

B.1.351 lineage

Another strain, B.1.351 (also known as 20C/501Y.V2), also shares the N501Y mutation. This variant was first detected in South Africa in October of 2020 and has since been found in more than 48 other countries since then.

The B.1.351 strain has the following key mutations:

- N501Y
- K417N
- E484K

This South African variant is believed to be about 50% more transmissible as compared to previous variants that have been identified in South Africa.

P.1 lineage

Another strain of note, 20J/501Y.V3, was first described in Japan by the National Institute of Infectious Diseases, thought to have arrived in the country from Brazil on the 6th of January. The variant has been traced back to Manaus, Brazil.

The strain is not thought to be more deadly but is more transmissible than the original strain of SARS-CoV-2.

The P.1 strain has the following key mutations:

- N501Y
- K417T
- E484K

The P.1 lineage is a branch of the B.1.1.248 lineage and bears 12 mutations in the spike protein, including the previously mentioned N501Y and an exchange of glutamic acid with lysine at position 484 (E484K). It is a close relative of the B.1.351 strain.

The E484K mutation had previously been reported in a different lineage originating in Brazil as early as the summer of 2020 (B.1.1.28).

B.1.427/B.1.429 lineage CAL.20C variant

The CAL.20C variant which spans the B.1.427 and B.1.429 lineages is believed to have emerged in California in May of 2020. Both of these variants are believed to be 20% more infectious than preexisting variant strains although do not seem to be spreading as fast as some variants like the B.1.1.7.

This strain has the following key mutations:

- L452R

B.1.525 and B1.526 lineages

In December of 2020, the B.1.525 variant was first found to be spreading throughout New York City. Like the B.1.1.7 lineage of SARS-CoV-2 variants, the B.1.525 variant also appears to have the same E484K

mutation and the H69-V70 deletion. In addition to these mutations, the B.1.525 variant lineage also carries the Q677H mutation.

In addition to the B.1.525 lineage, the B.1.526 lineage of variants has also been identified in New York City. Notably, the B.1.526 lineage appears in two forms; one with the E484K spike mutation, whereas the other form of this variant has the S477N mutation.

B.1.617 lineage

The B.1.617 strain has been dubbed the "double mutant virus" due to two of the concerning mutations it carries. These two key mutations are:

- E484Q
- L452R

The rapid rate at which this variant has spread across India indicates to some scientists that this variant is highly transmissible. This observation is largely due to the fact that the B.1.617 variant appears to have a greater prevalence as compared to the other variants that have been detected in India, such as the B.1.618 variant that was originally present in West Bengal.

As the B.1.617 variant continues to spread at an alarming rate in India, three different subtypes of this variant have been identified which include B.1.617.1, B.1.617.2, and the B.1.617.3 variants. As compared to the first subtype of this variant, data suggests that the B.1.617.2 variant has a growth rate advantage that has allowed for it to become the dominant subtype found in much of India.

Mutations of concern

The apparent spontaneity of the development of some of the key mutations that have been discussed here suggests that the virus could be experiencing convergent selection pressures around the globe, with the most transmissible forms outcompeting their cousins.

The current mutations of concern that may be aiding the spread of corona virus include:

D614G

The D614G mutation is of B.1 lineage and appeared in early 2020. This mutation quickly spread across the world and became dominant.

The D614G mutation is a missense mutation in which an altered single DNA base pair causes the substitution of aspartic acid (single-letter code: D) with glycine (single-letter code: G) in the protein that the mutated gene encodes.

N501Y

This mutation is present in several lineages including B.1.345, B.1.17, and P.1. This mutation changes the amino acid asparagine (N) to tyrosine (Y) at position 501 in the receptor-binding domain of the virus' spike protein, which may aid the virus in a bind to cells more tightly.

E484K or "Eek"

This spike protein mutation has been found in several lineages and may aid the virus in avoiding some antibody types. In it, there is an exchange of glutamic acid with lysine at position 484.

E484Q

This spike protein mutation is also mutated at position 484, with the exception that the glutamic acid is substituted with glutamine. This mutation is thought to increase immune evasion and ACE2 binding.

K417

This spike protein mutation has been found in several lineages, including P.1 and B.1.351. It is also thought to help the virus bind to cells more tightly.

This mutation is K417N in the B.1.351 strain, and K417T in the P.1 strain

L452R

The L452R spike protein mutation has appeared in several lineages. In this mutation, there is a leucine to arginine substitution at amino acid 452. The mutation is thought to increase immune evasion and ACE2 binding.

This mutation was observed in both the U.S. and Europe in 2020, before increasing in prevalence in January 2021, as it is notably present in the CAL.20C variant that has become widespread in California, particularly in Los Angeles. It is also notably present in the B.1.617 variant.

Notably, laboratory studies have found that specific monoclonal antibody treatments may not be as effective in treating COVID-19 caused by variants with the L452R or E484K mutations.

Q677

The Q677 mutation is located on the side of the SARS-CoV-2 spike protein, thereby suggesting that it may play a role in increasing the penetrability of the virus into human cells. To date, the Q777 mutation has been identified in several different SARS-CoV-2 variant lineages, seven of which have been identified in the United States. The Q677 variant has not yet been determined to be more infectious as compared to preexisting mutations.

Which regions of the SARS-CoV-2 genome mutate the most?

A large meta-study performed by Koyama, Platt & Parida (2020) gathered over 10,000 SARS-CoV-2 genomes worldwide and compared them to detect the most common mutations, identifying nearly 6,000 distinct variants.

The most divergent genome segment was ORF1ab, which is the largest by far as it occupies around a third of the genome. ORF1ab is transcribed into a multiprotein complex that is eventually cleaved into a number of nonstructural proteins that are involved in transcription. Some of these proteins are the target of anti-viral drugs remdesivir and favipiravir, which may be a cause for concern regarding the development of a strain against which these drugs have no effect.

The second most diverse region of the SARS-CoV-2 genome is around the spike protein, which must remain largely conserved in order to interact with ACE2. Some mutations, such as D364Y, have been reported to enhance the structural stability of the spike protein, increasing its affinity for the receptor. However, most are likely to lessen the virulence of the virus to such an extent that the lineage quickly dies off.

Conclusions

In this study it is observed that the strain of the variant B.1.617 has grown exponentially in India since the beginning of 2021. When we run the most frequent mutations in India, on the reference consensus B.1.617 India Variant, the level of the B.1.617 consensus reference variant genome is more than 6.6 times higher than that of the Wuhan SARS-CoV2 reference genome. Lab studies have shown that the B.1.617 variant can attach with more strength to the ACE-2 receptors, the site where the corona virus binds to our cells, than the earlier versions of the virus. The B.1.617 variant with increased transmissibility is likely to affect more children in the form of third wave that is going to be a greatest concern across the world.

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