L452M in spike glycoprotein indicative of zoonotic links of SARS-CoV-2 XBC.1

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Abstract

Mutations at positions 452 and 486 of the spike glycoprotein receptor binding domain (RBD) in the SARS-CoV-2 XBC.1 variant were analysed from the viewpoint of change in hydrophobicity and amino acid charge. A decrease in hydrophobicity due to mutations at positions 452 and 486 in the spike glycoprotein was observed, which might affect the infectivity of the XBC.1 variant. L452M and F486P improve the hACE2-RBD binding affinity, which might negatively impact the efficacy of vaccines against SARS-CoV-2, primarily based on spike glycoprotein. Notably, the mutation L452M in XBC.1 also indicates its probable zoonotic links.

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ABSTRACT

Mutations at positions 452 and 486 of the spike glycoprotein receptor binding domain (RBD) in the SARS-CoV-2 XBC.1 variant were analysed from the viewpoint of change in hydrophobicity and amino acid charge. A decrease in hydrophobicity due to mutations at positions 452 and 486 in the spike glycoprotein was observed, which might affect the infectivity of the XBC.1 variant. L452M and F486P improve the hACE2-RBD binding affinity, which might negatively impact the efficacy of vaccines against SARS-CoV-2, primarily based on spike glycoprotein. Notably, the mutation L452M in XBC.1 also indicates its probable zoonotic links.

BACKGROUND

XBC.1 variant of SARS-CoV-2 is showing an increasing trend in countries located in North America, Europe, Asia and Australia.[1]As per European Centre for Disease Prevention and Control, XBC.1 is designated as a variant under monitoring.[2] L452M and F486P are two important mutations in the XBC.1 spike protein within the receptor binding domain (RBD). It has been found that L452M and F486P enhance the infectivity; this may also impact the potency of SARS-CoV-2 vaccines which are based on spike protein.[3,4] Since the RBD-Human Angiotensin Converting Enzyme 2 (hACE2) interaction enables viral entry into the human

cells, SARS-CoV-2 infectivity may be affected by the substitution of amino acids in the spike protein RBD region.[4,5]

SPIKE GLYCOPROTEIN MUTATIONS AT POSITIONS 452 & 486

Position 452 is located in the receptor binding motif in the RBD, the amino acid substitution L452M will increase the size of the side chain of the spike protein RBD region.[6] Position 486 is pivotal in binding RBD to hACE2.[7] Positions 452 and 486 of the SARS-CoV-2 sublineages of omicron have been reported to be mutation prone; the mutational analysis of XBC.1 identified a unique mutation, L452M when compared with seventeen SARS-CoV-2 sublineages of omicron. In particular, BA.5, CH.1.1, BA.4.6, BA.4, BQ.1.1, BQ.1, BF.7 and XAY.2 were found to have L452R mutation (Figure).

Additionally, a rare mutation, F486P was found in the variants XBB.1.5, XAY.2, and XBC.1. This mutation is caused by two nucleotide polymorphisms in a single codon in comparison to the wild-type Wuhan strain. CH.1.1, XBB, BA.2.75.2, XBB.1 and XBB.2 have F486S mutation; and BQ.1.1, BA.4.6, BQ.1, BF.7, BA.5, and BA.4 have F486V mutation.

AMINO ACID HYDROPHOBICITY AFFECTS RBD-hACE2 BINDING AFFINITY

In the spike glycoprotein RBD positions at 452 and 486, the amino acids in the wild-type Wuhan-Hu-01 are leucine and phenylalanine, which are substituted by less hydrophobic amino acids methionine and proline in XBC.1, respectively. These mutations in XBC.1, indicate, that a selection pressure might be working towards acquiring the amino acids that are relatively less hydrophobic in spike glycoprotein. Kyte and Doolittle hydrophobicity index is considered for understanding the relative hydrophobicity.[8]

Hydrophobic interactions have a major role in stabilising the SARS-CoV-2 spike protein.[9] When a neutral and hydrophobic amino acid such as phenylalanine is substituted by a neutral and lesser hydrophobic amino acid such as proline at the position 486, this particular substitution might increase the RBD-hACE2 binding affinity. In addition, another substitution at the 452 position where a neutral and hydrophobic amino acid such as leucine is replaced by a neutral and lesser hydrophobic amino acid such as methionine may alter the RBD-hACE2 binding affinity.[10] Methionine substitution in XBC.1 spike glycoprotein at position 452 is predicted to increase the RBD-hACE2 binding affinity.[11] A general trend of increasing RBD-hACE2 binding affinity is observed when a neutral and less hydrophobic amino acid is incorporated. In contrast, there is a reduction in the binding affinity of RBD-hACE2 when a negatively charged and less hydrophobic amino acid is incorporated.

ZOONOTIC ORIGIN OF L452M IN XBC.1

The mutation L452M has been noticed in SARS-CoV-2 sequences collected from minks; and has been linked to zoonotic transmissions between humans and minks. However, the zoonotic transmissions were observed only when the L452M mutation co-occurred with F486L.[12] The binding affinity studies show that the co-occurring mutations L452M and F486L reduced the binding affinity between human ACE2 and RBD but resulted in increased binding between the mink ACE2 receptor and RBD of the spike glycoprotein.[13] In the case of XBC.1, the mutation L452M co-occurs with F486P, which might affect the RBD-hACE2 binding affinity. The cumulative effect of L452M and F486P on RBD-hACE2 binding affinity warrants further studies.

CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Shefali Rahangdale, Siddharth Singh Tomar, Ekant Tamboli, Sandhra Ravikumar, and Lekha Salsekar contributed to literature survey, analysis and interpretation, draft preparation. Dr. Krishna Khairnar: Conception, Manuscript editing, and revising.

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FIGURE LEGEND: (A) Mutational analysis of spike glycoprotein RBD region of SARS-CoV-2 Omicon. Hydrophobicity of amino acids according to the Kyte and Doolittle scale is represented as superscript. (B) Representation of RBD residues interacting specifically with the hACE2 receptor across 18 omicron sublineages.

Unique mutations are highlighted in red and hACE2 positions interacting with RBD are highlighted below the sequence in orange.