Original Article

E-protein variability in Zika virus strains: A possible new O-glycosylation site and its implications

Lokesh Kori,[1] Anshuman Chandra,[2] Labanya Mukhopadhyay,[1] Kanika Verma[3] & Nivedita Gupta[1]

[1]Division of Communicable Diseases, Indian Council of Medical Research, [2]School of Physical Science, Jawaharlal Nehru University and [3]Department of Molecular Epidemiology, ICMR-National Institute of Malaria Research, New Delhi, India

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Background and objectives: Zika virus (ZIKV) is a flavivirus transmitted by the bite of infected *Aedes* mosquito. In 2015-16, Brazil reported cases of ZIKV virus infection followed by Guillain-Barre syndrome and congenital birth defects. India has reported ZIKV virus infections sporadically since 2016, without adverse events. This prompted us to conduct this *in-silico* investigation and identify reasons for this variation. The objective was to study ZIKV envelope protein (E-protein) to identify possible mutations and their potential role in virus entry into the host cell.

Methods: Using multiple sequence alignments, we compared the genomic sequences from eleven ZIKV strains with maximum genomic data available in the NCBI database, followed by phylogenetic analysis. ZIKV E-protein structures with mutations were generated using AlphaFold and used for molecular dynamic simulation, followed by protein 3D structure and residues interaction analysis.

Results: We identified 2 major ZIKV clades - ZIKV Senegal strain (African lineage, Accession No. MF510857, 1984) is an ancestral strain representing one clade, while the remaining strains belong to the second major clade, with the Indian strain being closest to the Senegal strain genomically. The Senegal strain also has a significant mutation at residue no. 120 of the E-protein (Alanine to Threonine), which is absent in other strains.

Interpretation and conclusions: We found a mutation in the ZIKV Senegal strain at residue no. 120 (Alanine → Threonine), here Threonine is interacting with Serine residue at position 64. This interaction is known for post-translational O-glycosylation of E-protein, which may reduce the efficacy of envelope-based therapies. To the best of our knowledge, this is the first report of a putative O-glycosylation site on the E-protein of a ZIKV strain, which is an important therapeutic target, and our finding needs further in vitro validation.

Keywords E-protein, Flavivirus; O-glycosylation; Vector borne diseases; Zika virus

demonstrated that ZIKV infects the human