

Article

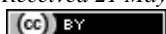
Open Reading Frame 4 protein as potential drug target for HEV: Structural evaluation through computational approaches

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Abstract

Hepatitis E virus (HEV) is the main cause of acute hepatitis worldwide. The viral infection caused by G1 HEV in pregnant women has become a major health concern in the past few years. The mechanism underlying the pathogenesis of viral infection in HEV G1 isolates is attributed to four different open-reading frames (ORFs) i.e., ORF1, ORF2, ORF3 and ORF4. The present analysis has considered ORF4 protein as the molecular target due to its intrinsic disorder propensity. Intrinsically disordered regions (IDRs) are regions in proteins that do not possess stable secondary and tertiary structure and are prevalent in eukaryotes. IDRs are found to be closely associated with numerous human diseases, for instance, Parkinson and Alzheimer disease. The extreme flexibility and random coiled conformations of IDR allow it to undergo protein-protein interaction (PPI). The 3-dimensional (3D) structures of the target protein were designed using homology modelling algorithms. The generated models were assessed through structure verification tool PROCHECK. In this paper, we provide an overview of ORF4 protein structure–function relationship and its involvement in several biological processes through PPIs. Our results suggest that ORF4 protein has the potential to act as drug molecule, thus can accelerate the process of drug designing strategies against HEV.

Keywords Open Reading Frame 4; intrinsically disordered region; drug target; secondary structure; 3D model.

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1 Introduction

Hepatitis E virus (HEV) is the major aetiological agent of Hepatitis E, also called enteric hepatitis (enteric means related to the intestines) infection. Worldwide, about 20 million HEV infections and 3.3 million symptomatic hepatitis E cases occur annually which results in 44,000 deaths (Hoofnagle et al., 2012; Kamar et al., 2017; Wedemeyer et al., 2012). HEV is a quasi-enveloped *Orthohepevirus*, with a single-strand, positive-sense RNA genome of around 7.2 kb in length and flanked with short 5' and 3' non-coding regions (NCR) (Meng, 2008; Mushahwar, 2008). Recently, a novel reading frame ORF4 has been identified in G1 of HEV entirely embedded within ORF1 in a different reading frame (Nair et al., 2016; Subramani et al., 2018).

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