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Extended Abstract

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Conserved epitopes of DENV structural and non-structural proteins for exploring universal vaccine targets

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Dengue is a severe emerging arthropod-borne viral disease occurring globally. Around two-fifths of the world's population or up to 3.9 billion people are at a risk of dengue infection. Infection induces a life-long protective immunity to the homologous serotype but confers only partial and transient protection against subsequent infection against other serotypes. Thus, there is a need for a vaccine which is capable of providing a lifelong protection against all the serotypes of dengue virus. In our study, comparative genomics of Dengue virus (DENV) was conducted to explore potential candidates for novel vaccine targets. From our analysis we successfully found 100% conserved epitopes in Envelope protein (RCPTQGE); NS3 (SAAQRRGR, PGTSGSPI); NS4A (QRTPQDNQL); NS4B (LQAKATREAQKRA) and NS5 proteins (QRGSGQV) in all DENV serotypes. Some serotype specific conserved motifs were also found in NS1, NS5, Capsid, PrM and Envelope proteins. Using comparative genomics and immune informatics approach, we could find conserved epitopes which can be explored as peptide vaccine candidates to combat dengue worldwide. Serotype-specific epitopes can also be exploited for rapid diagnostics. All ten proteins are explored to find the conserved epitopes in DENV serotypes, thus making it the most extensively studied viral genome so far. Dengue virus or as commonly called DENV is a single stranded RNA virus that infects approximately 390 million people each year, putting more than two-fifth of the world's population under the threat of this efficacious virus. The dengue fever has, thus become one of the most widespread disease. The virus belongs to the family Flaviviridae and genus Flavivirus . DENV is an arbovirus, having two known mosquito vectors Aedes aegypti and Aedes albopictus . The positive stranded RNA genome of dengue virus is of 10.7 Kb size and composed of three structural proteins (Envelope, Capsid, Membrane) and seven non-structural proteins (NS1, NS2A, NS2B,NS3, NS4A, NS4B, NS5). There are atleast four serotypes and they show 65% similarity in the genome structure. The dengue infection is caused by one of the four serotypes of DENV that are spread by Aedes mosquito. During primary infection, the body develops immune responses in the form of antibodies against the particular serotype attacked. But the main complexity of DENV arises during the secondary infection with another serotype, leading to serious version of dengue infection like Dengue Haemorrhagic fever (DHF) and Dengue Shock Syndrome (DSS). This is caused due to the antibodies produced during primary attack which complicate the secondary DENV infection by a phenomenon known as Antibody Dependent Enhancement (ADE). During ADE, there is a cross reaction between the antibodies of the primary infection and virus of secondary infection such that there is an increased infection in macrophages and monocytes. These challenges bring the importance of an archetypal dengue vaccine which can provide life time immunity against all the serotypes. Currently, the vaccine candidates that are under various stages of clinical trial are the live attenuated viruses, chimeric vaccine, recombinant vaccine with adjuvants, reverse vaccinology, purified and inactivated virions, subunit proteins and plasmid DNA. Among these, live attenuated DENGVAXIA or CYD-TDV, a tetravalent chimeric dengue vaccine, developed by Sanofi Pasteur in December 2015, is the first licensed vaccine in some Asian and Latin American countries. These clinical manifestations caused by the vaccine are ascribed to inefficiency of the vaccine in producing competent T- cells that protect against DENV disease. Moreover, the vaccine does not encode any non- structural proteins which are required by the virus to evade immune response of the host. All these studies imply that a vaccine that is tetravalent and simultaneously prevents antibody- dependent enhancement (ADE) needs to be designed urgently. These concerns led to the need for a relatively new technique of vaccine development i.e. Epitope or synthetic peptide based vaccines. As DENV has both structural and non-structural proteins for its viral activity, conserved epitopes may prove to be useful in designing synthetic peptide based vaccine. This can be easily initiated in today's time, as there is no dearth of information about genome sequences in the databases. A sum total of 23,622 partial sequences of structural and non-structural proteins of dengue virus were retrieved from NCBI. After retrieving, the sequences were aligned using multiple sequence alignment program CLUSTAL_X. These aligned sequence files were then used for further analysis. Sequences were used for detecting the speciesspecific signature sequences or motifs. Motifs were obtained for each serotype of DENV individually using an online tool multiple em for motif elicitation or MEME Suite . Motifs common for all serotypes were also obtained using the same method. In order to get a maximum number of motifs, the default setting was adjusted from 3 motifs to 10 motifs. The motifs were then analyzed for the presence of B cell epitopes. The linear B cell epitopes were found using BCPRED and BEPIPRED tools of immune epitope database with default settings. Bepipred used Hidden Markov model for the prediction of B cell epitopes. The immunogenicity of each epitope was checked using Kolaskar and Tangaonkar antigenicity method with a default threshold value 0.9. Hydrophilicity of the antigenic epitopes, required to check the accessibility were found using Parker Hydrophilicity method at a threshold value of 3.448. Epitopes were checked for their surface accessibility using Emini surface accessibility method with a threshold value of 1.00. Flexibility and Beta turns were checked using Karplus and Schulz Flexibility and Chou and Fasman Beta-turn methods respectively, with a threshold of 1.00 for both.