Int. J. Pharm. Investigation, 2026; 16(3):1143-1151.
https://www.jpionline.org

Original Article

Structural Biology and Viral Genetics of the DENV-1 NS5 Methyltransferase Domain: Functional Insights and Epitope Mapping

Ghadeer Bukhari*

Biological Sciences Department, College of Science and Arts, Rabigh Campus, King Abdulaziz University, Jeddah, SAUDI ARABIA.

ABSTRACT

Background: The NS5 protein in Dengue Virus Serotype-1 (DENV-1) is a multifunctional enzyme that is crucial for the virus to reproduce and evade the immune system. One important part of NS5 is the methyltransferase (MTase) domain, which modifies the viral RNA genome by adding methyl groups to the 5' cap structure. This modification protects the genome from host cell exonucleases and helps with translation. **Materials and Methods:** In this study, we used several computational methods to analyze the structure and function of the NS5 methyltransferase domain. **Results:** We looked at its secondary structure and disordered regions with feature mapping and SDISOPRED3 plots, predicted protein-protein interactions using DeepMeta PSICOV, and identified possible immune recognition sites through epitope prediction. These sites could be important for developing vaccines and therapies. **Conclusion:** Overall, our analyses highlight key features of the NS5 methyltransferase domain and show its potential as a target for treating DENV-1 infection.

Keywords: DeepMeta, Dengue virus, DOMPred, Epitope, Functional analysis, NS5 methyltransferase, WHO.

Correspondence:
Dr. Ghadeer Bukhari
Biological Sciences Department, College of Science and Arts, Rabigh Campus,
King Abdulaziz University, Jeddah-21589,
SAUDI ARABIA.
Email: gfbukhari@kau.edu.sa

Received: 18-02-2026;
Revised: 06-04-2026;
Accepted: 25-05-2026.

INTRODUCTION

A significant threat to global health, the Dengue Virus (DENV) is the cause of dengue fever, a disease transmitted by mosquitoes. The primary vectors of the virus are *Aedes* mosquitoes, specifically *Aedes aegypti* and *Aedes albopictus* (Lessa *et al.*, 2023; Pourzangiabadi *et al.*, 2025). According to Gubler (2011) and Messina *et al.* (2019), there are four different serotypes of DENV: DENV-1, DENV-2, DENV-3, and DENV-4. These serotypes can cause mild dengue fever as well as more severe illnesses, such as Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) (Gubler, 2011; Messina *et al.*, 2019). The most common of the four serotypes, Dengue Virus Serotype-1 (DENV-1), has been linked to multiple outbreaks, especially in tropical and subtropical areas where *Aedes mosquitoes* thrive World Health Organization (WHO). DENV-1 causes a significant percentage of dengue illnesses, and the clinical severity of these infections varies based on host immunity and genetic variables (Rodenhuis-Zybert *et al.*, 2010; Messina *et al.*, 2019; WHO, 2020). A single-stranded RNA virus, the DENV-1 genome is a member of the *Flaviviridae* family, which also includes other viruses with significant medical applications, such as the Zika, West Nile, and Yellow Fever viruses (Murugesan *et al.*, 2020; Madere *et al.*, 2025). With a genomic size of about 10.7 kb, DENV-1 encodes a polyprotein that may be broken down into seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) and three structural proteins (Capsid [C], Membrane [M], and Envelope [E]) (WHO, 2020; Yacoub *et al.*, 2013; Lindenbach *et al.*, 2001). The increasing incidence of dengue outbreaks across tropical and subtropical regions, the absence of specific antiviral treatments, and a partially effective vaccine (Dengvaxia) underscore the need for continued research into better preventive and therapeutic strategies. Understanding the molecular biology, pathogenesis, and immune responses associated with DENV-1 is critical for developing more effective vaccines, therapeutics, and vector control measures (de Almeida *et al.*, 2025; Guzman *et al.*, 2016).

The Dengue Virus Serotype-1 (DENV-1) NS5 protein is a crucial enzyme in the virus's reproduction cycle and a prime target for antiviral treatment approaches. This protein is an enzyme with many functions essential for viral genome replication and immune system evasion. An RNA-dependent RNA polymerase (RdRp) domain and a Methyltransferase (MTase) domain are the two main functional domains of NS5, and both are necessary for the viral genome's production and maturation (Sinha *et al.*, 2024; Norazharuddin *et al.*, 2018; Pires *et al.*, 2018). NS5

DOI: 10.5530/ijpi.20260265

Publishing Partner : Manuscript Technomedia. [www.mstechnomedia.com]

methyltransferase domain is responsible for adding methyl groups to the viral RNA genome. For the virus to survive and replicate within the host, the 5' cap structure on the viral RNA must develop, and this mechanism is essential to that process. In addition to protecting the viral RNA from degradation by the host exonucleases, the 5' cap promotes the host translation machinery recognition of it. This capping mechanism is crucial for the peace and effective translation of viral RNA within the host cell (Zhao *et al*., 2017; Zhao *et al*., 2015; Younas *et al*., 2020). A mesmerizing target for creating antiviral medications is the NS5 methyltransferase, an enzyme highly conserved across Dengue Virus serotypes. Blocking the methyltransferase activity may result in the destruction of the viral genome or the failure to form the 5' cap, which would impair viral replication and strengthen immunological responses against the virus (Mazri *et al*., 2024; Younas *et al*., 2020). In this manuscript, the NS5 methyltransferase domain (NS5) in DENV-1 highlights its structural and functional importance in the viral life cycle and its potential as a target for therapeutic intervention.

MATERIALS AND METHODS

Overview on Dengue Virus Serotype-1 (DENV-1) Structure

Dengue Virus Serotype-1 (DENV-1) is part of the *Flavivirus* genus and the *Flaviviridae* family. Its structure includes envelope (E), membrane (M), and capsid (C) proteins, an RNA genome, and non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5). Tools such as PANTHER, Prosite, Pfam, SMART, and InterProScan help provide a detailed domain map of DENV-1.

Amino acid Sequence Feature Map, plot and SDISOPRED3 Plot

To map the amino acid sequence of the DENV-1 virus's NS5-methyltransferase domain, the server located at http://bioinf.cs.ucl.ac.uk/psipred/ was used. The sequence schematic is displayed by mapping position-dependent feature predictions using the provided tool (Teramoto *et al*., 2017). We also highlighted the NS5-methyltransferase domain of the DENV-1 virus, which has several coils, strands, and helices (http://bioinf.cs.ucl.ac.uk/psipred/&uuid=828a4c6e-fd53-11ef-a479-00163e100466).

DISOPRED3 is a popular program for identifying intrinsically disordered regions (IDRs) in protein sequences. Although intrinsically disordered proteins (IDPs) or regions (IDRs) do not have a stable three-dimensional structure in physiological settings, they are crucial for cellular processes like transcription, transduction, and molecular recognition (Trivedi *et al*., 2022). Disordered regions are those that have a high risk of being disordered. Ordered regions are locations where the protein sequence is anticipated to fold into a distinct three-dimensional structure (http://bioinf.cs.ucl.ac.uk/psipred/).

DeepMeta PSICOV Contact Plot, DMP Fold and Dom Prediction

DeepMeta PSICOV is a deep learning method that predicts protein contact maps using evolutionary and co-evolutionary data. This approach helps show how parts of viral proteins, such as the Envelope (E) protein, Non-structural protein, or Capsid (C) protein, interact in DENV-1 (Dengue Virus Serotype 1) (Wang *et al*., 2017; Kandathil *et al*., 2019; Jones *et al*., 2015). By creating a contact map, DeepMeta PSICOV illustrates the spatial relationships between amino acids, which is useful for 3D modeling and understanding the function of viral proteins. Furthermore, DeepMeta PSICOV outputs can serve as input or reference data for other protein structure prediction tools such as DMPFold and DOMPred, integrating information across methods.

DMPFold needs the primary amino acid sequence in FASTA format. Since the quality of the input sequence affects the prediction results, ensure the sequence is complete and error-free (DMPFold Web Server). DMPFold can utilize contact maps generated by DeepMeta PSICOV to improve accuracy. DOMPred uses machine learning models trained on known domain annotations to predict domain boundaries and functional regions in proteins. It also benefits from information provided by tools like DeepMeta PSICOV, as evolutionary and contact data complement domain boundary predictions. DOMPred relies on evolutionary data and sequence properties to identify folded domains and disordered regions in a protein sequence (Cai *et al*., 2006).

Amino acid sequence and its composition

A protein amino acid sequence, a list of amino acids, each represented by a three-letter code, determines its structure, function, and interactions with other molecules. To analyze the DENV-1 serotype 1 sequence, which contains 262 amino acids, we used the ExPASy Server (https://web.expasy.org/protparam/), obtaining an aligned sequence and the total count for each amino acid (Gasteiger *et al*., 2005; Boeckmann *et al*., 2003). These outcomes are compiled in an Excel file (CSV format), which shows the full amino acid (a.a) composition along with a chart showing the proportion and distribution of each amino acid in the sequence (Apweiler *et al*., 2004).

Predicting of antibody epitope

Antibody epitopes are specific regions of a pathogen's protein (usually an antigen) recognized by the immune system's antibodies. Identifying these epitopes is crucial for vaccine design, diagnostics, and therapeutic antibody development. The prediction of epitopes from a protein sequence can be done through computational methods (http://tools.immuneepitope.org).

The Emini Surface Accessibility Prediction is used to predict the surface accessibility of amino acids in a protein. It helps to identify which protein regions are likely to be exposed on the surface and, therefore, are more likely to be involved in interactions such as antibody binding or protein-protein interactions. For Dengue Virus Serotype 1 (DENV-1), applying this prediction can help in understanding the immune evasion strategies of the virus and also identify potential epitopes for vaccine development (Larsen *et al*., 2006).

Possible Molecular Function Predictions

The DENV-1 genome encodes several structural and non-structural proteins, each with a distinct molecular function. These include the virus's pathogenicity, immunological evasion, and replication. The molecular roles of the DENV-1 proteins are summarized below. We forecast the molecular function using an available tool (server at http://bioinf.cs.ucl.ac.uk/psipred/).

RESULTS

Structural Analysis of DENV-1 Protein Domains

The Dengue Virus Serotype 1 (DENV-1) structure is essential for understanding its infection mechanism, viral entry, assembly, and pathogenesis. Like other members of the *Flavivirus* family, the virus has a relatively simple but well-defined structure consisting of three major structural proteins (capsid, envelope, and membrane) and several non-structural proteins involved in replication and immune evasion.

The non-structural proteins are involved in viral replication and immune modulation. They include NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5. These proteins primarily function within the host cell to facilitate the replication of the viral genome and to counteract host immune responses. Here, we focused on the NS5-methyltransferase domain of the DENV-1 virus (Figure 1).

Study of sequence map, Sequence plot, Disopred3 Plot

To predict features such as secondary structure, disordered regions, and functional sites in the amino acid sequence of the Dengue Virus Serotype-1 (DENV-1), we can generate Amino Acid Sequence Feature Maps and DISOPRED3 plots. Position-dependent feature predictions are mapped onto the sequence schematic below (Figures 2A-2C).

The line height of the Phosphorylation and Glycosylation features reflects the confidence of the residue prediction. In parallel, we also predicted a helix with a blue symbol and sheet with a red aero symbol (Figure 2A). The NS5-methyltransferase domain of the DENV-1 virus domain reveals strands, α-helix, and coil (Figure 2B). These methodologies relied on the helix-or sheet-molding tendencies of individual amino acids, primarily combined with rules for assessing the free energy of confining flexible structural segments of the NS5-methyltransferase domain. As the NS-5 methyltransferase domain is a catalytic domain, it is likely to have both ordered and disordered regions. For instance, structural regions may correspond to the areas responsible for RNA binding or catalysis, while disordered regions might be involved in flexibility and protein-protein interactions (Figure 2C).

DeepMeta PSICOV Contact, DMP Fold and Dom Prediction

We present the DeepMeta PSICOV contact prediction results for Dengue Virus Serotype 1 (DENV-1) proteins. These results predict which residues in the protein structure are in contact. Knowing these contacts helps us understand how the protein folds in three dimensions, how proteins interact with each other, and how viral proteins function. The predictions use a contact map from the DeepMeta PSICOV model, which applies deep learning to identify long-range residue contacts using multiple sequence alignments (Figure 3A).

We present the results of DMP Fold Prediction for fundamental Dengue Virus Serotype 1 (DENV-1) proteins, with a focus on predicting 3D protein structures. The Deep Learning-based Molecular Property Fold (DMP Fold) prediction method utilizes advanced machine learning algorithms to predict the most likely fold or 3D structure of proteins based on their amino acid sequences. Understanding the protein folding process is crucial for identifying functional domains, protein-protein interactions, and mechanisms of viral pathogenesis (Figure 3B). Domain prediction is a powerful tool to identify conserved structural and functional regions within a protein sequence. These domains are critical for understanding the protein's biological function, protein-protein interactions, and their role in the viral life cycle. Putative domain boundaries located in PSI-BLAST alignment profile: Number of predicted domains by DPS: 2Domain Boundary locations predicted DPS: 149 Putative domain boundaries located in PSI-BLAST alignment profile: Number of predicted domains by DPS: 2. Domain Boundary locations predicted DPS: 149 (Figure 3C).

Amino Acid Composition and prediction epitopes of DENV-1 Proteins

The amino acid (a.a) composition analysis involves determining the frequency and distribution of each amino acid within a given sequence (protein), which provides insights into the structure (protein), functional roles, and biological activities. By examining the abundance of specific amino acids, we can infer protein stability, functionality, and how specific residues contribute to protein-protein interactions (Figure 4A). Surface Accessibility Profile: The plot generated by the Emini method provides a graphical representation where the y-axis corresponds to the Relative Solvent Accessibility (RSA), and the x-axis corresponds to the position of the amino acid in the protein sequence. The results showed that the Center position was 3, the threshold was 1.000, the average was 1.000, the minimum was 0.073, and the

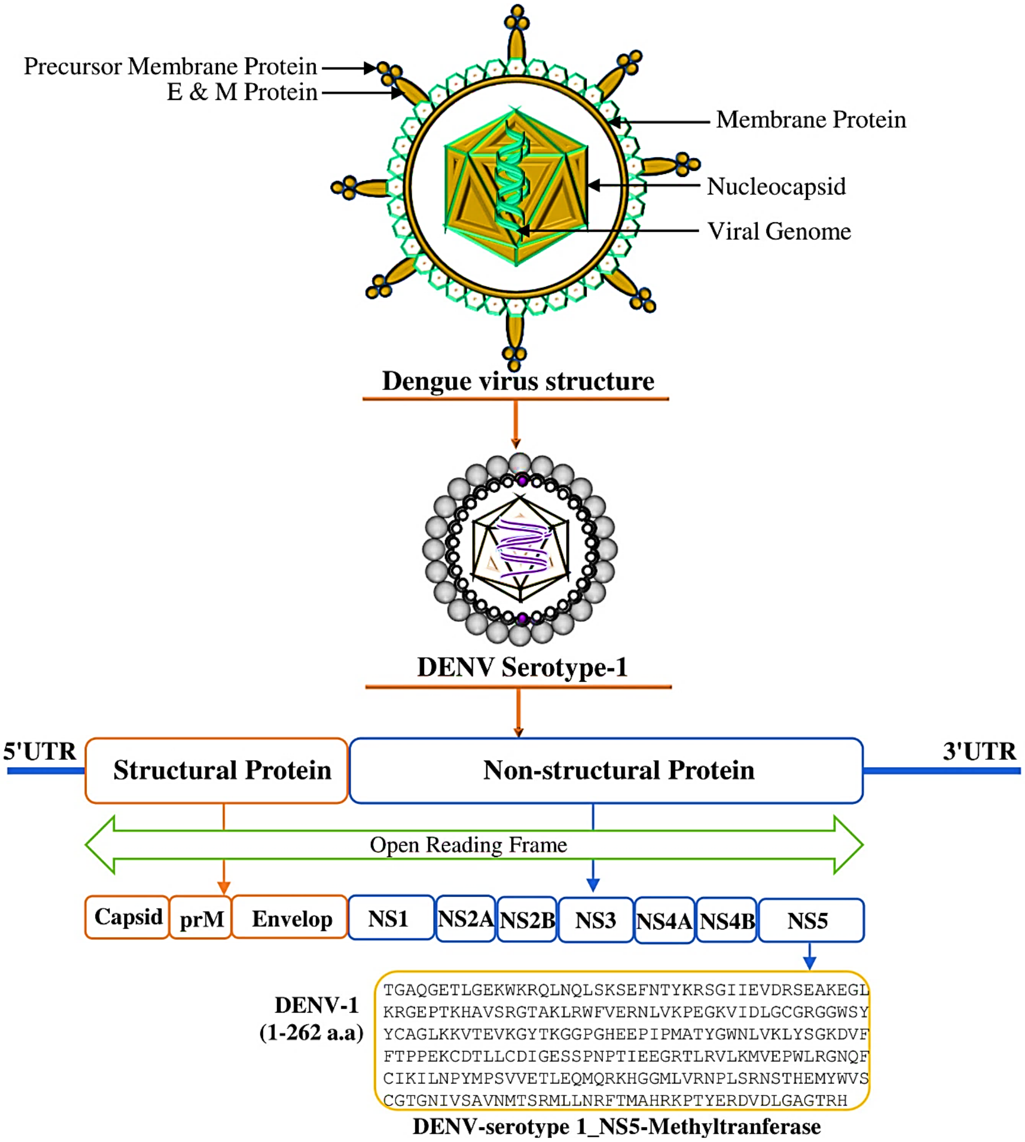

Figure 1: Diagrammatic representation of the Dengue Serotype Virus-1 (DENV-1) structure, highlighting the membrane protein, nucleocapsid, viral genome and others. Three structural and seven non-structural proteins are formed by digesting the DENV RNA genome and polyprotein. Untranslated region, or UTR. Amino acid sequence (1-262) of NS5-methyltransferase domain of DENV-1 virus.

maximum was 4.823 (Figure 4B). For a protein like DENV-1's Envelope protein (E protein), the plot may show peaks at certain positions, indicating high surface accessibility. At the same time, other regions may have low peaks, indicating buried residues that are not accessible. In parallel, we plotted the bar graph representing the predicted peptide sequences with peptide length (Figure 4C).

Functional Insights into DENV-1

Viral Replication and Transcription (NS3: The NS3 protein is essential for viral RNA replication and polymerase activity) is one of the several molecular roles of DENV-1 serotype one that we have anticipated. It plays a role in the formation of new viral genomes for packaging into progeny virions, the regulation of apoptosis (NS4B: The NS4B protein has been found to inhibit apoptosis or programmed cell death), the maintenance of infected cells for viral replication, and the activity of enzymes (SAM-dependent methylation: A methyl group is transferred from S-Adenosylmethionine (SAM) to the 5' guanosine of the viral RNA by the NS5 methyltransferase domain. Methyltransferase Activity adds methyl groups to the viral RNA, RNA Cap Formation alters the viral RNA's 5' cap, Host Immune Evasion obstructs host immune sensors from recognizing the viral RNA, and RNA Stability protects the viral RNA from being broken down by host exonucleases (Figure 5).

DISCUSSION

Dengue Virus Serotype-1 (DENV-1) is one of four types of Dengue virus, part of the *Flaviviridae* family, and the *Flavivirus* genus. It is specifically spread by *Aedes* mosquitoes, especially

Aedes aegypti (Murugesan *et al.*, 2020). DENV-1 causes illnesses that range from mild dengue fever to severe forms such as Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) (Halstead., 2014). Understanding the virus's structure, how it causes disease, how it avoids the immune system, and how it interacts with the host is important for developing effective vaccines and antiviral treatments (Chappell *et al.*, 2015; Alwabli, 2024; Alzahrani *et al.*, 2024; Alwabli *et al.*, 2024). After binding to a receptor, the virus enters endosomes within the cell. The acidic environment in the endosome alters the shape of the protein (E). This transformation enables the viral envelope to connect with the endosomal membrane, thereby releasing the viral RNA into the cytoplasm (Modis *et al.*, 2005). DENV-1 and other *flaviviruses* are experienced at evading the host immune system. They reach this by modulating the host immune response and using various immune modulation strategies. For example, the NS1 protein is released during infection and helps the virus avoid immune detection by interacting with the complement system and blocking the immune response (Muller *et al.*, 2017; Alwabli *et al.*, 2017; Alwabli *et al.*, 2019; Alwabli *et al.*, 2017). The SDISOPRED3 tool predicts disordered regions in proteins based on their amino acid sequences. Many viral proteins, including those from DENV-1, contain disordered regions crucial for their function. These regions assist with protein-protein interactions, enzyme activity, and communication between the virus and host cells (Sinha *et al.*, 2024; Nasar *et al.*, 2020). In DENV-1, SDISOPRED3 predicts that the NS5 protein, especially its methyltransferase domain, contains disordered regions that may be key to viral replication. These flexible regions enable the virus to interact with host cell machinery by binding to various partners and changing shape during infection (Kubler *et al.*, 2019; Alwabli *et al.*, 2019; Alwabli *et al.*, 2019). DeepMeta PSICOV contact prediction reveals that specific regions of the NS5 methyltransferase domain and the E protein interact with host proteins, such as eukaryotic translation Initiation Factor 4G (eIF4G), as well as with other viral components. This interaction helps explain how the virus uses the host's machinery to replicate. PSICOV also identifies structural changes in viral proteins when they bind to host cell receptors

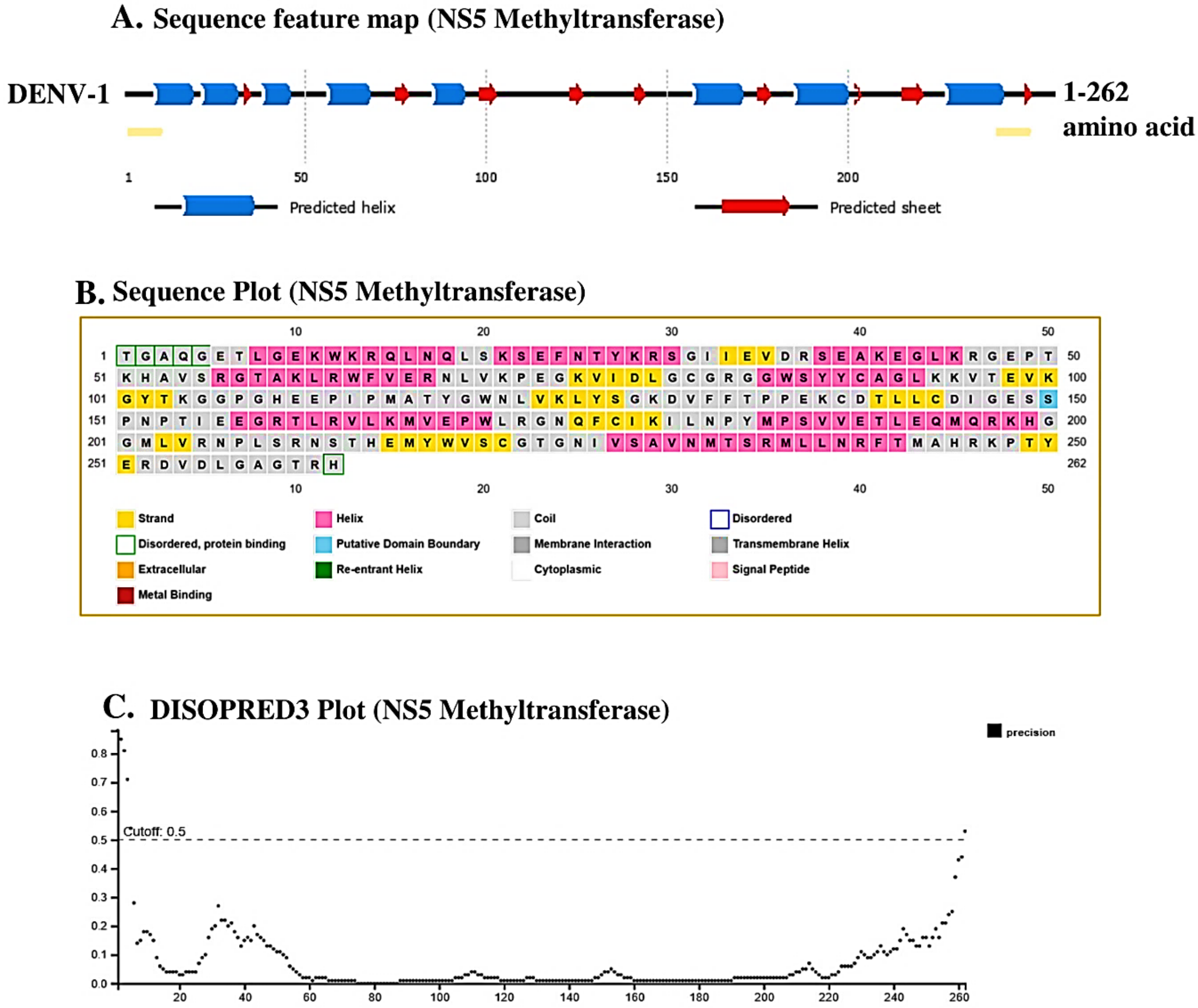

Figure 2: (A) Analysis of sequence map (B) Sequence plot (C) Disopred3 Plot NS5-methyltransferase domain of DENV-1 virus.

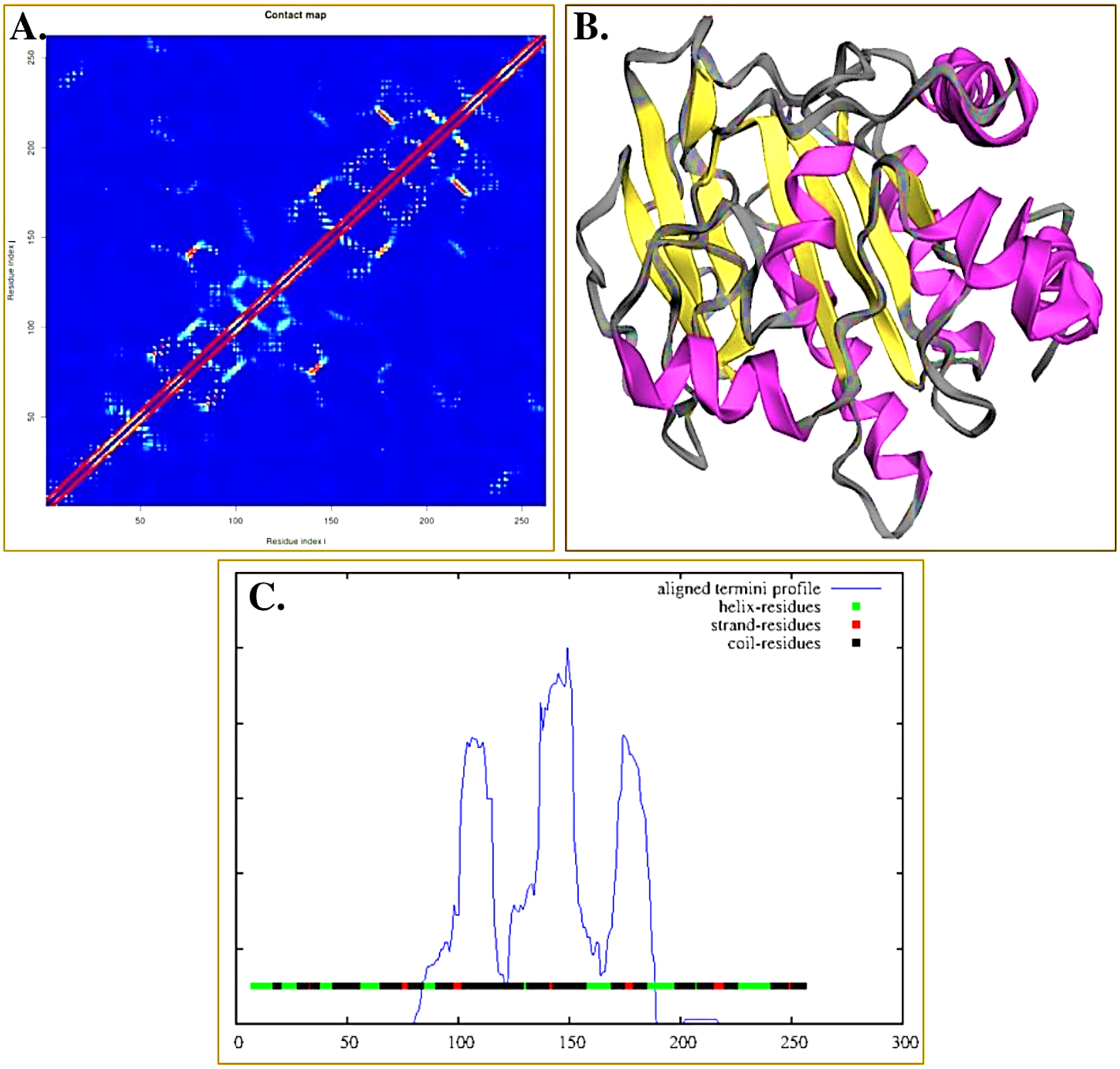

Figure 3: (A) Deep Meta PSICOV Contact Plot (B) DMP Fold prediction (C) Dom Pred.

or shift shape during cell entry (Chen *et al.*, 2019; Muhammad *et al.*, 2023; Afaq *et al.*, 2020; Afaq *et al.*, 2020). Domain prediction identifies functional parts of a protein that are responsible for binding, catalysis, or maintaining structural stability (Panchenko *et al.*, 2018). For DENV-1, tools such as InterPro and Pfam indicate that the NS5 protein contains important domains, including a methyltransferase domain and an RNA-dependent RNA polymerase domain. The E protein has a fusion domain (Panchenko *et al.*, 2018; Shahbaaz *et al.*, 2020; Al-Samghan *et al.*, 2020; Zhang *et al.*, 2017; Lee *et al.*, 2023). DeepMeta PSICOV provides information about protein-protein interactions, especially in NS5, which is crucial for viral replication. NS5 has two main domains: methyltransferase and RNA-dependent RNA polymerase (RdRp). PSICOV predicts that these domains interact with other viral proteins, such as NS3 and host factors including eIF4G and FliA, which are involved in replication. PSICOV contact maps reveal the arrangement of different protein parts, aiding in folding and shape changes. These interactions are significant for keeping the stability and activity of viral enzymes and may serve as targets for antiviral drugs (Jones, *et al.*, 2015). Epitope prediction identifies parts of viral proteins recognized by the immune system, notably B cells and T cells. Epitopes are small protein sections that antibodies or T-cell receptors can bind to, making them necessary for vaccine and therapeutic antibody design. Predicting epitopes in DENV-1 proteins helps locate possible immune response targets. Identifying both linear and conformational B-cell epitopes in DENV-1 proteins is crucial for developing vaccines that induce protective immunity. Tools like BepiPred (Larsen *et al.*, 2006) and IEDB can predict which areas are probable to interact with antibodies (Ponomarenko *et al.*, 2008). For illustration, epitopes in the protein (E), particularly in the fusion domain or domain III, have been identified as viable targets for antibodies (neutralizing antibodies. These epitopes often contain many hydrophilic amino acids (aa), making them accessible to the immune system on the virus's surface (Harrison *et al.*, 2014). DENV-1, the main cause of dengue fever, is a *flavivirus* that presents challenges in understanding disease mechanisms and developing effective vaccines and treatments.

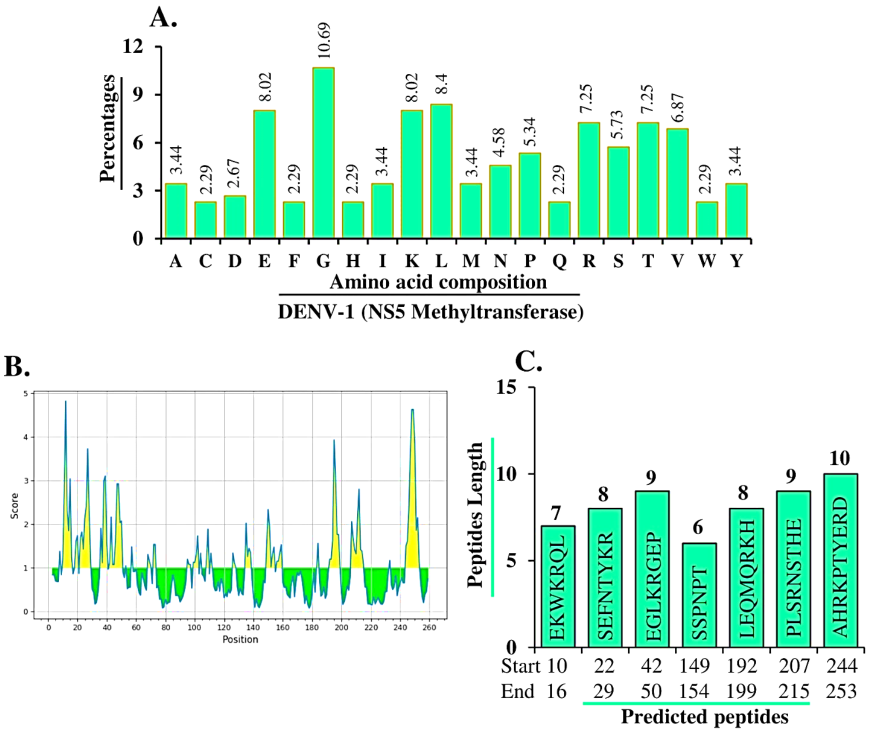

Figure 4: (A) Amino acid composition and their parentage (B) Antibody Epitope Prediction graph (C) Predicted peptide sequence with peptide length.

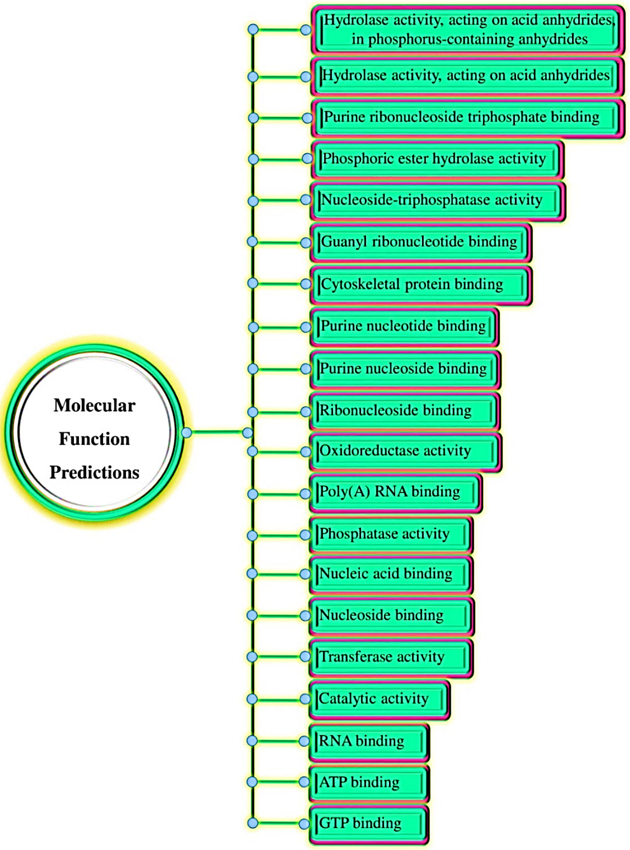

Figure 5: Molecular Function Predictions of dengue serotype virus-1 (DENV-1).

Studying its molecular functions, particularly those of key viral proteins, is essential for finding new ways to control the disease (Lee *et al.*, 2017).

Applications of the Research

One of the most significant applications of this research is in antiviral drug discovery targeting Dengue Virus type 1 (DENV-1). Detailed structural and functional characterization of the NS5 Methyltransferase (MTase) domain provides essential insights for structure-based drug design, enabling the identification of conserved binding pockets and functionally critical regions that can be exploited therapeutically. Such knowledge directly supports molecular docking, virtual screening, and molecular dynamics simulations aimed at discovering small-molecule inhibitors that disrupt viral RNA capping and replication (Alwabli and Ishtiaq, 2021; Alwabli *et al.*, 2025). Furthermore, integrating phytochemical screening and pharmacokinetic evaluation enhances the potential for identifying safe and effective antiviral candidates (Alwabli *et al.*, 2025). The computational strategies demonstrated here are also transferable to other viral enzymes, as shown in related studies on *flaviviruses* and coronaviruses, reinforcing the broader relevance of this approach in antiviral therapeutics (Alwabli, 2022; Alwabli, 2023).

CONCLUSION

Understanding the molecular functions of Dengue Virus Serotype 1 (DENV-1) helps explain how it replicates and interacts with host cells. Using DISOPRED3, we found that the NS5 methyltransferase (NS5-MTase) domain has flexible regions that may bind to viral RNA or host proteins, which could be useful for drug development. By analyzing amino acids and predicting epitopes, we identified sites that are vulnerable or help the virus avoid the immune system. Studying the structures of key proteins (E, NS1, NS3, & NS5) helps in designing vaccines and treatments by identifying key functional regions and B- and T-cell epitopes. Emini surface accessibility points out exposed residues that could be targeted by antibodies or vaccines. Predicting related biological processes shows how DENV-1 uses host pathways to replicate, avoid immune responses, and change cell signaling, which can guide the development of replication inhibitors, immune modulators, and vaccines.

ACKNOWLEDGEMENT

This project was funded by the Deanship of Scientific Research (DSR) at King Abdulaziz University, Jeddah, under grant no. (GPIP: 2034-665-2024). The authors, therefore, acknowledge with thanks DSR for technical and financial support.

ABBREVIATIONS

DENV: Dengue virus; **DHF:** Dengue hemorrhagic fever; **DSS:** Dengue shock syndrome; **WHO:** World Health Organization; **RdRp:** RNA-dependent RNA polymerase; **MTase:** Methyltransferase; **IDRs:** Intrinsically disordered regions; **SAM:** S-adenosylmethionine; **a.a:** Amino acid; **RSA:** Relative solvent accessibility; **eIF4G:** Eukaryotic translation initiation factor 4G.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FUNDING

This project is funded with a grant No. (GPIP: 2034-665-2024).

AUTHORS CONTRIBUTION

Ghadeer Bukhari: Conceptualization; Methodology; Data curation; Formal analysis; Investigation; Writing original draft.

GENERATIVE AI STATEMENT

The author declares that generative AI tools, including Grammarly and QuillBot, were used solely to enhance the language and clarity of this work, and takes full responsibility for the accuracy and integrity of the content.

SUMMARY

Currently studying how Dengue virus serotype 1 functions at the molecular level. They are looking at how it interacts with host cells, identifying potential drug targets, and determining which parts of the virus the immune system can target most easily. The team is also focusing on important proteins, mapping B- and T-cell epitopes, and predicting related biological processes. Their goal is to support the development of new replication inhibitors, immune modulators, and vaccines.

REFERENCES

Afaq, S., Atiya, A., Malik, A., Alwabli, A. S., Alzahrani, D. A., Al-Solami, H. M., *et al.* (2020). Analysis of methyltransferase (MTase) domain from Zika virus (ZIKV). Bioinformation, 16(3), 229-235.

Afaq, S., Malik, A., Akhtar, M. S., Alwabli, A. S., Alzahrani, D. A., Al-Solami, H. M., *et al.* (2020). Analysis of predicted proteasomal cleavages in the methyltransferase domain from JEV. Bioinformation, 16(3), 223-228.

Al-Samghan, A. S., Alwabli, A. S., Abadi, M., Alsaleem, S. A., Anbari, D. M., Alomari, A. S., *et al.* (2020). From sequence analysis of DPP-4 to molecular docking-based searching of its inhibitors. Bioinformation, 16(6), 444-451.

Alwabli, A. S. (2024). Deciphering the molecular landscape of dengue infection: Insights from gene expression profiling and protein interactions. The Microbe, 5, 100195.

Alwabli, A. S., Al-Attas, S. G., Mohammed, N., Alhebshi, A., Alkenani, N., Al-Ghmady, K., & Qadri, I. (2019). Gene expression profiling and functional annotation of dengue virus. International Journal of Drug Development & Research, 11(3), 25-29.

Alwabli, A. S., Al-Attas, S. G., Mohammed, N., Alhebshi, A., Alkenani, N., Al-Ghmady, K., & Qadri, I. (2019). Methyltransferase activity of dengue RNA virus using purified protein. International Journal of Drug Development & Research, 11(1).

Alwabli, A. S., Alattas, S. G., Alhebshi, A., Mohammed, N., Alkenani, N., Al-Ghmady, K., & Qadri, I. (2019). Pharmacological modulation of flavivirus methyltransferase activity of dengue virus. Indian Journal of Pharmaceutical Education and Research, 53(3S).

Alwabli, A. S., Bukhari, G., Balubaid, M., Tarique, M., Mahmoud, S. R., Aljedani, J., & Ramady, A. (2024). Analyzing thermal influences on protein microtubules in eukaryotic cells through nonlocal elasticity modeling. Cattle Practice, 32(12).

Alwabli, A. S., Khattab, E. A., & Farag, A. G. (2017). Biological, serological and molecular characterization of pepper mild mottle virus isolated from Saudi Arabia. Research Journal of Infectious Diseases, 5(1), 1-11.

Alwabli, A. S., Khattab, E. A., & Farag, A. G. (2017). Purification and production of antiserum against pepper mild mottle virus isolated from Saudi Arabia. Research Journal of Biotechnology, 12(12), 14-19.

Alwabli, A. S., & Ishtiaq, Q. (2021). Identification of possible inhibitor molecule against NS5 MTase and RdRp protein of dengue virus in Saudi Arabia. Journal of King Saud University -Science, 33(5), 101493.

Alwabli, A. S., Balubaid, M., & Tarique, M. (2025). Exploring phytocompounds' interaction with multi-serotype dengue virus NS5-MTase. Journal of Biomolecular Structure and Dynamics (In Press).

Alwabli, A. S. (2023). Novobiocin as a potent inhibitor of Japanese encephalitis virus envelope protein: Docking and fluorescence studies. Journal of Molecular Graphics and Modelling, 117, 108306.

Alwabli, A. S. (2022). Lead identification against 3C-like protease of SARS-CoV-2 using virtual screening and molecular dynamics simulation. Journal of Molecular Structure, 1264, 133213.

Alzahrani, D. A., Abulfaraj, A. A., Mostafa, H. M., Mahmoud, S. R., Alwabli, A. S., & Aljedani, J. (2024). Thermal response of protein microtubules: A nonlocal elasticity perspective on cellular mechanics. Cattle Practice, 32(12).

Apweiler, R., Bairoch, A., Wu, C. H., *et al.* (2004). UniProt: The universal protein knowledgebase. Nucleic Acids Research, 32, D115-D119.

Boeckmann, B., Bairoch, A., Apweiler, R., *et al.* (2003). The Swiss-Prot protein knowledgebase and its supplement TrEMBL in 2003. Nucleic Acids Research, 31, 354-370.

Chappell, J. D., & Dermody, T. S. (2015). Biology of viruses and viral diseases. In J. E. Bennett, R. Dolin, & M. J. Blaser (Eds.),Mandell, Douglas, and Bennett's principles and practice of infectious diseases (8th ed., pp. 1681-1693.e4).

Cai, Y., *et al.* (2006). DOMPred: A domain-based disordered protein prediction method. Bioinformatics, 22(14), 1762-1768.

Chen, Y., Chen, S., Li, K., *et al.* (2019). Overdosage of balanced protein complexes reduces proliferation rate in aneuploid cells. Cell Systems, 9(2), 129-142.e5.

de Almeida, M. T., Merighi, D. G. S., Visnardi, A. B., Boneto Gonçalves, C. A., Amorim, V. M. F., Ferrari, A. S. A., de Souza, A. S., & Guzzo, C. R. (2025). Latin America's dengue outbreak poses a global health threat. Viruses, 17(1), 57.

Gasteiger, E., Hoogland, C., Gattiker, A., *et al.* (2005). Protein identification and analysis tools on the ExPASy server. In J. M. Walker (Ed.),The Proteomics Protocols Handbook (pp. 571-607). Humana Press.

Gubler, D. J. (2011). Dengue and dengue hemorrhagic fever. Clinical Microbiology Reviews, 24(3), 1-23.

Guzman, M. G., Harris, E., & Halstead, S. B. (2016). The interplay of dengue virus and host immune system. Nature Reviews Microbiology, 14(2), 107-120.

Halstead, S. B. (2014). Dengue virus–mosquito interactions. Viral Immunology, 27(6), 263-271.

Harrison, S. C., Clements, D., & Modis, Y. (2005). A molecular model of the dengue virus envelope protein. The EMBO Journal, 24(3), 414-423.

Jones, D. T., & Cozzetto, D. (2015). DeepMetaPSICOV: A novel deep learning approach for protein contact prediction. PNAS, 112(4), 656-661.

Kubler, K., Richelieu, J. M., & Karakoc, E. (2019). The methyltransferase domain of dengue virus NS5 as a target for therapeutic intervention. Frontiers in Microbiology, 10, 1495.

Kandathil, S. M., Greener, J. G., & Jones, D. T. (2019). Prediction of interresidue contacts with DeepMetaPSICOV in CASP13. Proteins: Structure, Function, and Bioinformatics 87, 1092-1099

Lessa, C. L. S., Hodel, K. V. S., Gonçalves, M. S., & Machado, B. A. S. (2023). Dengue as a disease threatening global health: A narrative review focusing on Latin America and Brazil. Tropical Medicine and Infectious Disease, 8(5), 241.

Larsen, J. E., Lund, O., & Nielsen, M. (2006). Improved method for predicting linear B-cell epitopes. Immunome Research, 2(2), 1745-7580.

Lee, J. W., *et al.* (2017). Development of protease inhibitors for dengue virus infections. Antiviral Research, 143, 100-112.

Lee, J. Y., *et al.* (2023). DeepFold: Enhancing protein structure prediction. Bioinformatics, 39(12), btad712.

Lindenbach, B. D., & Thiel, H. J. (2001). Flaviviridae: The viruses and their replication. In D. M. Knipe & P. M. Howley (Eds.),Fields Virology (4th ed., pp. 991–1041). Lippincott Williams & Wilkins.

Mazri, R., Ouassaf, M., Kerassa, A., & Alhatlani, B. Y. (2024). Exploring potential therapeutics: Targeting dengue virus NS5 through molecular docking, ADMET profiling, and DFT analysis. Chemical Physics Impact, 8, 100468.

Madere, F. S., Andrade da Silva, A. V., Okeze, E., *et al.* (2025). Flavivirus infections and diagnostic challenges for dengue, West Nile and Zika viruses. npj Viruses, 3, 36.

Messina, J. P., *et al.* (2019). The global distribution and burden of dengue. Nature, 530(7588), 162-167.

Modis, Y., Ogata, S., Clements, D., & Harrison, S. C. (2005). A molecular model of the dengue virus envelope protein. The EMBO Journal, 24(3), 414-423.

Muhammad Bilal Khan, *et al.* (2023). Dengue overview: An updated systematic review. Journal of Infection and Public Health, 16(10), 1625-1642.

Murugesan, A., & Manoharan, M. (2020). Dengue virus. In M. M. Ennaji (Ed.),Emerging and reemerging viral pathogens: Volume 1: Fundamental and basic virology aspects of human, animal and plant pathogens, 281-359.

Muller, D. A., Depelsenaire, A. C., & Young, P. R. (2017). Clinical and laboratory diagnosis of dengue virus infection. Journal of Infectious Diseases, 215(Suppl. 2), S89-S95.

Norazharuddin, H., & Lai, N. S. (2018). Roles and prospects of dengue virus non-structural proteins as antiviral targets: An easy digest. Malaysian Journal of Medical Sciences, 25(5), 6-15.

Nasar, S., Rashid, N., & Iftikhar, S. (2020). Dengue proteins with their role in pathogenesis, and strategies for developing an effective anti-dengue treatment: A review. Journal of Medical Virology, 92(8), 941-955.

Panchenko, A. R., *et al.* (2018). Protein domain prediction and functional annotation. Bioinformatics, 34(2), 345-354.

Pires, D., & Fonseca, F. (2018). Structural and functional analysis of dengue virus NS5 methyltransferase. Viruses, 10(12), 675.

Ponomarenko, J. V., *et al.* (2008). The Immune Epitope Database and Analysis Resource: From vision to blueprint. PLOS Biology, 6(5), e1000047.

Pourzangiabadi, M., Najafi, H., Fallah, A., Goudarzi, A., & Pouladi, I. (2025). Dengue virus: Etiology, epidemiology, pathobiology, and developments in diagnosis and control—A comprehensive review. Infection, Genetics and Evolution, 127, 105710.

Rodenhuis-Zybert, I. A., Wilschut, J., & Smit, J. M. (2010). Dengue virus life cycle: Viral and host factors modulating infectivity. Cellular and Molecular Life Sciences, 67(16), 2773-2786.

Shahbaaz, M., *et al.* (2020). Functional and structural analysis of predicted proteins obtained from Homo sapiens' minisatellite 33.15-tagged transcript pAKT-45 variants. BioMed Research International, 2020, 2562950.

Sinha, S., Singh, K., Ravi Kumar, Y. S., *et al.* (2024). Dengue virus pathogenesis and host molecular machineries. Journal of Biomedical Science, 31, 43.

Teramoto, T., Balasubramanian, A., Choi, K. H., & Padmanabhan, R. (2017). Serotype-specific interactions among functional domains of dengue virus 2 nonstructural proteins (NS) 5 and NS3 are crucial for viral RNA replication. *Journal of Biological Chemistry, 292*(23), 9465-9479.

Trivedi, R., & Nagarajaram, H. A. (2022). Intrinsically disordered proteins: An overview. International Journal of Molecular Sciences, 23(22), 14050.

World Health Organization. (2020). Dengue and severe dengue. World Health Organization.

Wang, S., Sun, S., Li, Z., Zhang, R., & Xu, J. (2017). Accurate de novo prediction of protein contact map by ultra-deep learning model. PLoS Computational Biology, 13(1), e1005324.

Yacoub, S., & Wilder-Smith, A. (2013). Dengue: Epidemiology, clinical features, and management. Public Health, 127(5), 288-297.

Younas, M., Liu, C., & Anwar, M. (2020). Molecular characterization of dengue virus type-1 and its interaction with host immune response. International Journal of Molecular Sciences, 21(18), 6621.

Zhao, Y., Soh, T. S., Lim, S. P., Chung, K. Y., Swaminathan, K., Vasudevan, S. G., Shi, P. Y., Lescar, J., & Luo, D. (2015). Molecular basis for specific viral RNA recognition and 2′-O-ribose methylation by the dengue virus nonstructural protein 5 (NS5). Proceedings of the National Academy of Sciences of the United States of America, 112(48), 14834-14839.

Zhao, B., Yi, G., Du, F., *et al.* (2017). Structure and function of the Zika virus full-length NS5 protein. Nature Communications, 8, 14762.

Zhang, Y., *et al.* (2017). DMPfold prediction: Toward higher accuracy in protein structure prediction. Nature Methods, 14(4), 423-429.

Cite this article: Bukhari G. Structural Biology and Viral Genetics of the DENV-1 NS5 Methyltransferase Domain: Functional Insights and Epitope Mapping. Int. J. Pharm. Investigation. 2026;16(3):1143-51.