

LCMV Interaction Changes with T192M Mutation in Alpha-Dystroglycan

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Abstract Limb girdle muscular dystrophy (OMIM: 613818) is a severe disease in humans, which broadly affects brain development. The disease is caused by T192M mutation in the protein alpha-dystroglycan (α -DG). α -DG is an important component of dystrophin–dystroglycan complex which links extracellular matrices with actin cytoskeleton and thereby maintains signalling cascades essential for the development of tissues and organs. The mutation T192M in α -DG hampers proper glycosylation of α -DG thereby developing limb girdle muscular dystrophy. Prototype virus for Old World Arenaviruses (OWV), Lymphocytic Choriomeningitis virus (LCMV) also uses this α -DG as host cell receptor and invades the host cell causing a disease called Lymphocytic choriomeningitis, an infection to meninges. Thereby, interaction of α -DG and LCMV has become an interesting object of study to predict the mode of the disease onset. In our current work, we have used homology modelling, molecular docking and molecular dynamics (MD) with temperature variation. We have identified significant structural differences between wild type (WT) and mutant (MT) α -DG in terms of spatiotemporal orientations of amino acids. This change in the folding patterns of the WT and MT α -DG has brought forth a different interaction pattern of the WT and MT α -DG with GP1 protein from LCMV as reflected in our docking simulations. Further MD simulations with the complexes over tropical and temperate environment have revealed that MT- α -DG-LCMV GP1 complex is relatively more stable than the wild type counterpart. It has also been found that LCMV GP1 has interacted strongly with mutant α -DG. Our studies therefore has shed light on the structure and molecular interaction pattern of LCMV with MT α -DG and also indicate a possibility of T192M mutant in α -DG making the receptor to interact strongly with LCMV GP1. These insights also provide clues to develop possible therapeutic approaches.

Keywords Homology modelling • Molecular dynamics • Limb girdle muscular dystrophy • Viral infection-drug design

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Abbreviations

DG	Dystroglycan
MDDGC9	Muscular Dystrophy, Dystroglycanopathy, Type C9
OMIM	Online Mendelian Inheritance in Man
PDB	Protein Data Bank
RMSD	Root Mean Square Deviation
WT	Wildtype
MT	Mutated

Highlights

1. T192M mutation causes changes in alpha-dystroglycan structure.
2. Interaction between Lymphocytic Choriomeningitis Virus (LCMV) with its receptor alpha-dystroglycan changes due to the mutation.
3. Molecular dynamics run with temperature variation shows interaction of LCMV with mutated receptor is stronger than the wild type receptor.

1 Introduction

Dystroglycan (DG) is a cell surface receptor and it belongs to dystrophin–dystroglycan complex which links extracellular matrices with cellular actin cytoskeleton [1]. Cellular actin cytoskeleton plays crucial role in development of tissues, organs not only by providing mechanical strengths to cells but also by taking active part in regulating macromolecular events [2] required for proper development [3]. Matured DG protein is composed of two subunits: alpha-dystroglycan (α -DG), the extracellular part of DG that interacts and receives signals from extracellular proteins like laminin, perlecan, argin, etc. and beta dystroglycan (β -DG), which remains bound to cell membrane [1]. This β -DG is linked with cellular dystrophin, which is an active actin binding protein [4]. The protein α -DG contains a mucin like region sandwiched between its N terminal and C terminal globular parts. This mucin rich region is essential for the proper glycosylation and functioning of α -DG [1]. Reportedly, a point mutation T192M in α -DG causes limb girdle muscular dystrophy, MDDGC9 (OMIM: 613818) affecting brain and nervous system growth resulting in severe cognitive impairments, mental retardation and delayed motor development [5, 6]. This mutation actually hampers LARGE (a transacetylase) mediated glycosylation leading to the disease onset. This signifies the role of α -DG in development and muscle strength.

Interestingly, α -DG also serves as a receptor to a large class of arenaviridae (AV), Old World viruses (OWV) [7]. OWVs invade host system by its preglycoprotein complex which has three major components: N terminal stable signal peptide (SSP), followed by glycoprotein G1 (GP1 ~ 42 kDa) and glycoprotein G2 (GP2 ~ 35 kDa) domains [7]. These viruses interact with the N terminal few amino acids and mucin

rich region of α -DG via their GP1 for attachment and fusion to the host system. Some of these AVs are also causative agents of diseases like lassa fever, Bolivian hemorrhagic fever, lymphocytic choriomeningitis (LCM), etc. causing significant mortality in affected human populations [8]. The prototype for OWV, Lymphocytic Choriomeningitis Virus (LCMV) causing LCM, a chronic asymptomatic, lifelong infection of meninges which is the membrane to protect central nervous systems [9, 10]. This has tempted us to study the molecular interaction pattern of α -DG and LCMV GP1. Although detailed studies have been carried out on LCMV regarding its global distribution, pathogenicity, residues essential for its interaction with α -DG [8], the insight to its molecular interaction with MT α -DG is still not deciphered. Therefore, we have ventured into the prediction of molecular aspects of disease propagation. We have taken a homology modelling approach to construct the model of LCMV GP1 domain and thereafter have docked this model with wild type (WT α -DG) and T192M mutant (MT α -DG) forms of α -DG separately. Our initial studies [6] with α -DG structures have also revealed that the mutant structure differs significantly in terms of its surface hydrophobicity in vicinity to the mutation site, 192. That is why we have focused on the structural changes occurring in the vicinity of mutation site and its effect on the binding orientation of LCMV GP1 with MT α -DG to elucidate the effect of the above-mentioned mutation. Molecular docking and subsequent molecular mechanistic simulations for the first time have revealed that MT α -DG has increased numbers of intermolecular hydrogen and hydrophobic bonds with LCMV GP1 establishing a stable interaction. Further we have employed MD with elevated temperature to monitor the changes in this interaction pattern. This study therefore for the first time sheds some light into the scenario where MT- α -DG interacts with LCMV. And we have observed the pattern indeed changed with mutated receptor protein. In future, this work will be helpful in designing some effective therapeutic approaches to defeat the virus borne disease.

2 Materials and Methods

2.1 Template Search

First, the sequence of LCMV GP1 domain, comprising amino acid residues 88–241, was extracted from UniprotKB (id: E2D674). This was then used as input sequence to search for the template in FUGUE [11] and pdb [12] using PSI-BLAST [13]. In both the cases, the A chain of crystal structure of envelope glycoprotein Machupo virus GP1 (PDB code: 2WFO) was obtained as the closest match.

2.2 Homology Modelling

This structure was then used as template to construct homology model for LCMV GP1 using modbase [14] web server with sequence-sequence, profile-sequence

(PSI-BLAST) and sequence-profile (Modeller Built-Profile) methods. Since the template is a model of New World virus- Machupo virus GP1, the modelling of our desired protein was not so straightforward. So, alternatively, model for this region (amino acid residues 88–241) has also been constructed using I-TASSER and RaptorX model building servers independently. Both these servers used 2WFO as the template. The models so generated were then superimposed on the previously built model to generate a consensus report (Supplementary File 1). All models were tested with Verify 3D [15] and PROCHECK [16]. We have also denatured the structure completely taking it up to 373 K starting from 273 K, then have allowed it to cool down to 273 K. And the structures were then superimposed in order to check for the folding accuracy. The Root Mean Square Deviation (RMSD) for these two superimposed files have been found to be 0.8 Å (Supplementary File 2) which implies that they are indeed identical and the folding patterns are conserved.

2.3 Molecular Docking

Next, we used this model to dock with WT α -DG and MT α -DG [6] separately using Z dock [17], PyDock [18] and Patchdock [19]. Docked complexes with best score and lower energy were selected and there were total 25 docked complexes (5 from Z dock, 10 from Pydock and 10 from Fire Dock) for each type of complex, i.e. WT- α -DG with LCMV and MT- α -DG with LCMV. Resultant docked complexes were then energy minimized keeping their backbones fixed to ensure proper interactions. 800 cycles of conjugate gradient energy minimization steps were applied with CHARMM [20] force field until the structure reached a final derivative of 0.01 kcal/mole. After each minimization, the structures were verified with Verify3D and PROCHECK. Further analyses of the docked complexes were done using Discovery Studio (DS) package version 2.5 and Protein Interaction Calculator [21]. Binding sites were detected with analyse binding site tool from DS for all the docked complexes to validate the docking process. Finally, the complexes with the lowest energy profile and with binding sites consensus with literature [8, 10] have been selected for wild type and mutated complexes. The complexes were then further subjected to minimization in explicit solvent system with CHARMM force field. Dielectric constant of the molecular surface was kept 80 as of periodic water bound condition.

2.4 Molecular Dynamics Simulations

Minimized complexes then were brought to elevated tropical temperatures (i.e. 300–320 K) and 10,000 time step of production run was performed in each of the cases keeping pressure constant. The conformational changes were recorded and plotted against time.

3 Results

3.1 The Conformation of MT α -DG Contributes to Altered Interaction with LCMV GP1

Our studies [6] with the models of both WT and MT α -DG initially have figured out that mutant structure has more buried surfaces than that of its wild type form. In order to investigate further the art of interactions, we have docked LCMV GP1 with WT and MT α -DG, separately. Analyses of docked pattern of the models clearly have reflected that there are indeed significant differences both in terms of amino acid residues involved in interaction as well as the spatiotemporal orientation of LCMV GP1, docked with either WT or MT α -DG (Fig. 1a). As mentioned earlier, the focus of our study was the immediate vicinity of mutation site at the amino acid residue position 192. And we have marked those amino acid residues 88–96 of LCMV GP1 have successfully interacted with a groove formed by amino acid residues 142–192 of α -DG (Fig. 1b). We have attempted to analyse the total number of intermolecular hydrogen bonds (H-bond) and hydrophobic interactions (HPI) formed between LCMV GP1 and α -DG in both the cases, in two different systems, i.e. discovery studio 2.5 and protein interaction calculator. Normalized average values of the bonds formed have been used to generate a graphical view (Fig. 1c) which reflected that LCMV-GP1 docked with MT α -DG had more numbers of H-Bonds and HPI interactions than the bonds formed for its docked model with WT- α -DG (left panel, Fig. 1c). Hydrogen bonds and hydrophobic interactions are the non-covalent interactions which are meant to stabilize the overall interaction occurring between two proteins [22]. Disturbance in these bonds will definitely affect the binding. Studies with the structures in further details have marked this dispute to be largely contributed by a huge structural change in mutant form of α -DG in vicinity to the mutation site (Met 192) that has resulted in a new space for LCMV GP1 interaction and also has created potentially altered kinks among few residues (arrows, Fig. 1d, e). Superimpositions of models of WT and MT- α -DG, minimized with either vacuum [6] or explicit solvent condition (Supplementary File 3) have revealed that there indeed exist structural differences between the two structures.

3.2 Identical Amino Acids Bent Differentially to Give a New Conformation to Mutant α -DG

Further assessment of the afore mentioned portion of α -DG has identified amino acid stretch 166–171 of α -DG to be the key to these disputes. The relative bends and positioning of these residues have formed a surface which is more closed or buried in MT α -DG than that of its wild type form (Fig. 2a). Surprisingly, dihedral angles between the adjacent residues in this patch, i.e. Ser166-Val167, Val167-Arg168,

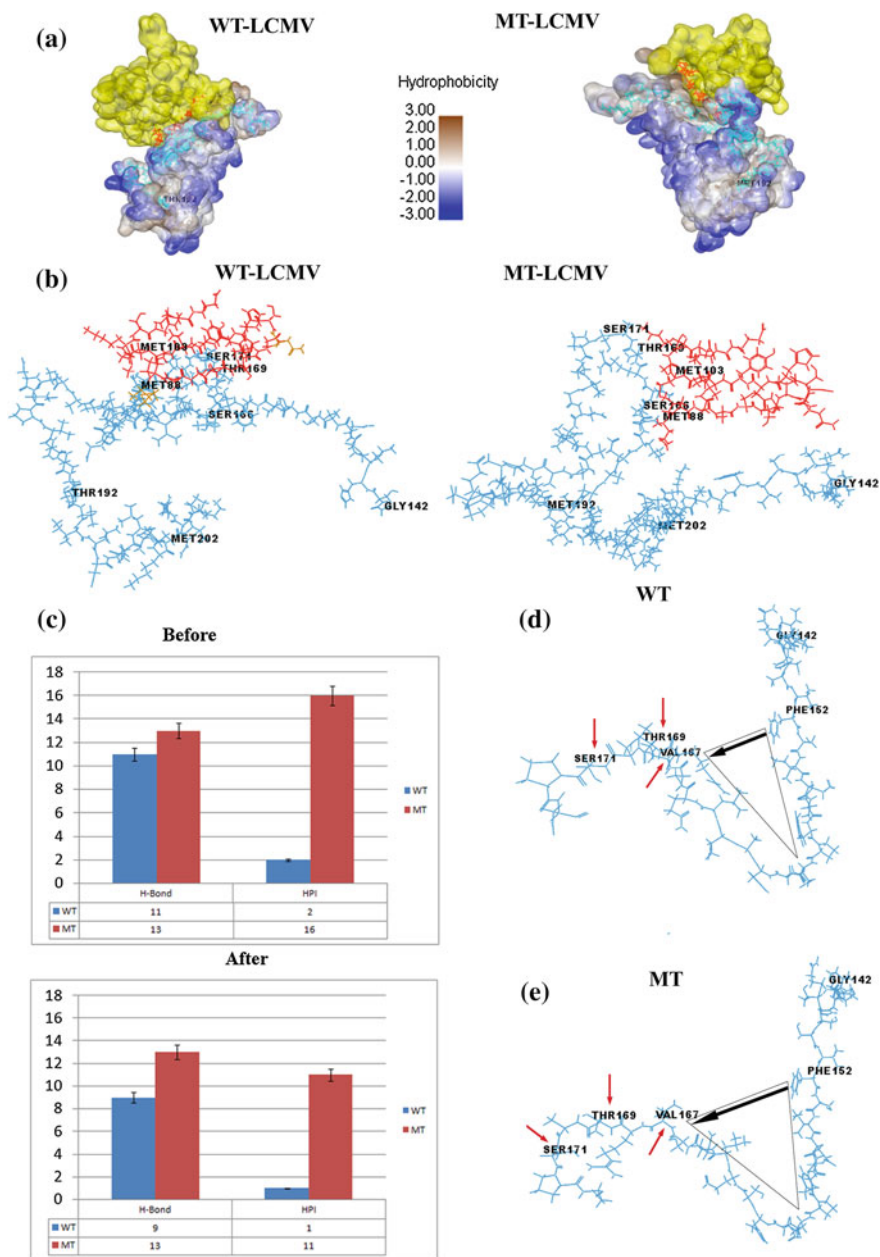


Fig. 1 LCMV GPI exhibited a different spatiotemporal orientation when interacted with MT α -DG. **a** Docked structures of LCMV GPI (red backbone, yellow surface) with WT- α -DG (blue backbone, left panel) and with MT α -DG (blue backbone, right panel). The common interacting portion has been shown with red backbone representation. **b** Amino acids in the vicinity of mutation site 192nd position and the different orientation of the docked complex. **c** Differences in intermolecular hydrogen bond and hydrophobic interactions have been shown. **d, e** Structural differences between WT and MT α -DG that open up an alternative binding site in case of mutated structure

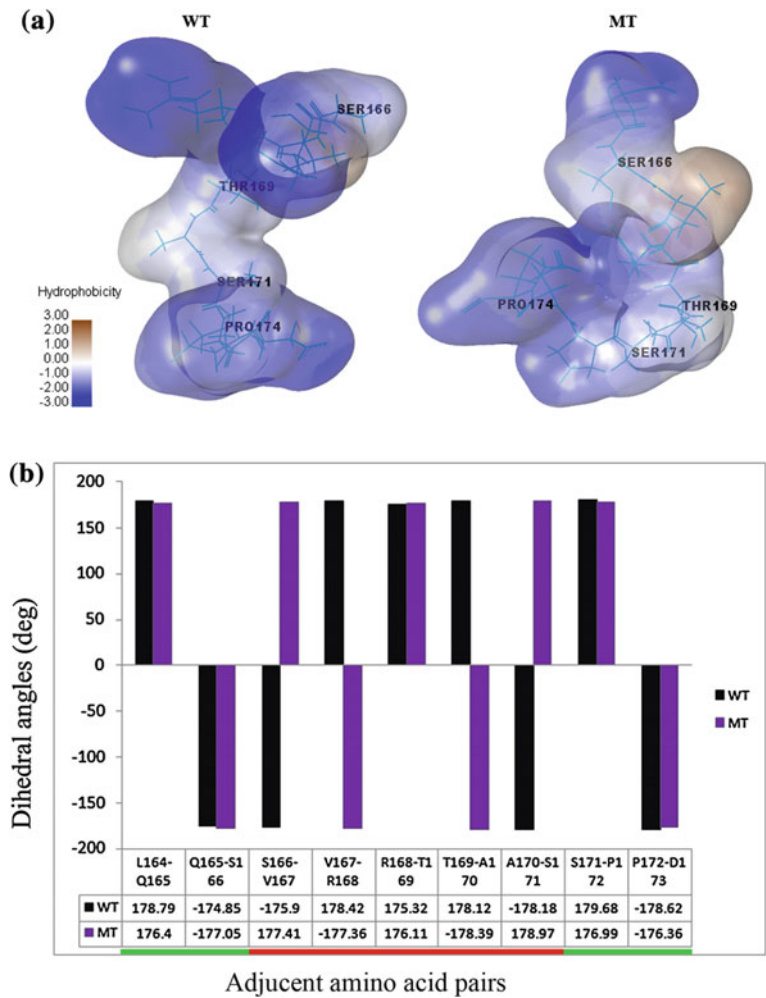


Fig. 2 Unusual kinks in amino acid pairs burying the surface in MT α -DG. **a** Different surface hydrophobicity between WT and MT α -DG making the interaction groove more buried. **b** The change in dihedral angles contributing to altered kinks in MT α -DG

Thr169-Ala170 and Ala170-Ser171, have possessed almost 180° change in two structures of α -DG (Fig. 2b). The corresponding changes of the angles are: Ser166-Val167 (-175.90) $\rightarrow$ (177.41), Val167-Arg168 (178.42) $\rightarrow$ (-177.36), Thr169-Ala170 (178.12) $\rightarrow$ (-178.39) and Ala170-Ser171 (-178.18) $\rightarrow$ (178.97) from WT $\rightarrow$ MT α -DG. Only amino acid pair Arg168-Thr169 (175.32 $\rightarrow$ 176.11) has similar dihedral angle in both the forms of α -DG.

3.3 Tropical Temperature Alters MT α -DG and LCMV GP1 Interactions

Lymphocytic choriomeningitis virus appears everywhere due to the large distribution of its host house mouse, rodents except for the Antarctica [23]. The serological prevalence of the virus has been reported to be centralized in Africa, but disease distribution occurs worldwide. Studies with patients suffering from lymphocytic choriomeningitis have revealed that this disease is prevalent in temperate zone [23]. Moreover, majority of Old World viral diseases occur at tropical and temperate regions [24]. So, we have employed MD run with a temperature range 27–47 °C so that we can monitor the changes in the interaction occurring between the receptor, α -DG and its ligand, LCMV-GP1. Changes in RMSD of the conformations over time in three different temperatures, i.e. 27, 37 and 47 °C (300, 310 and 320 K, respectively) have clearly demonstrated that the complex of MT- α -DG and LCMV-GP1 shows less alteration in RMSD with temperature change than the complex of WT- α -DG and LCMV-GP1 does. In other words, the interaction between MT- α -DG and LCMV-GP1 is much more stable than its wild type counterpart (Fig. 3).

4 Discussions

LCM, an infection of meninges which serve as a protective membrane for central nervous system, is developed due to the invasion of its causative agent LCMV to host system via α -DG, a host cell surface receptor and this interaction is largely counted on LARGE mediated proper glycosylation of matured α -DG. Additionally,

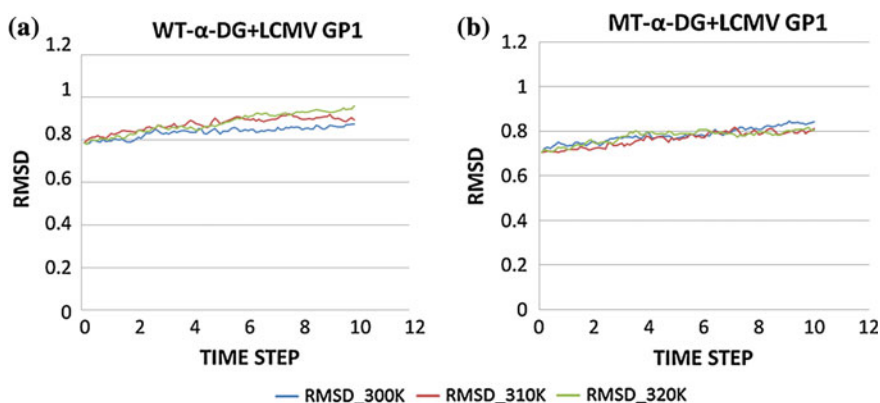


Fig. 3 Effect of temperature on the interactions. **a, b** RMSD versus Time plots exhibit that in case of the complex of LCMV GP1 with wild-type receptor has shown greater deviation in RMSD for the conformations (**a**). On the contrary, complex of LCMV GP1 with the mutated receptor has less conformational changes (**b**) with change in temperatures

a mutant form of this α -DG (T192M) hampers LARGE mediated glycosylation resulting in alteration in signalling cascade essential for proper brain development. Patients with T192M mutation in α -DG develop severe mental retardations along with cognitive impairment. These common features of the two diseases, i.e. dependence on LARGE, involvement of α -DG, proper glycosylation and above all affecting nervous system, brain, have made the interaction of LCMV and α -DG an invincible study object to us. In our current work, we have found that amino acid stretches 166–171 of α -DG in the close vicinity to mutation site of Met 192 have contributed to structural bends which finally have created relatively more buried conformation for MT α -DG than that of wild type one. Majority of amino acid pairs have almost 180° orientation difference in their dihedral angles which imply that replacement of polar Thr 192 with non-polar Met has conferred structural strains to the positional orientations of its upstream and downstream amino acids. Because of this, mutant form of α -DG has possessed a buried conformation with those amino acid stretches which otherwise have a widened window in the wild type α -DG. And this has forced LCMV GP1 to occupy a different space for interaction with MT α -DG. But this has been proven to be advantageous for the interaction of the two participating proteins since interaction of LCMV GP1 with α -DG has more main backbone based H-Bonds formed, compared to its interaction with WT- α -DG. And these same results have also been reflected with solvent explicit models. Interestingly, this result has an indication of likelihood of susceptibility to LCMV infection in the presence of the T192M mutation. This has urged us to look for the possible fold pattern of LCMV GP1 that can serve as a potential blocking site to restrict the disease propagation. In our study, as we already have shown that stretch of amino acids 88–96 of LCMV GP1 has remained a common mediator of interactions for both WT and MT α -DG and it also has possessed a particular fold pattern. In future, analysis of this structure will enlighten a path for developing novel therapeutic approaches against this viral transmission. Moreover, temperature-based variation on the conformations from our MD run have revealed that the interaction of LCMV GP1 and α -DG with T192M mutation is significantly stable than the interaction of LCMV GP1 with the wild type receptor. In conclusion, our experiments have shed lights on the molecular interactions of LCMV GP1 with MT α -DG, for the first time of its kind. Experimental results, here, have shown that structural aberrations in mutant α -DG owing to the altered bends in its amino acids residues have lead to changes in its interaction pattern with LCMV GP1. But this changed spatiotemporal orientation finally has resulted in strong binding of LCMV GP1 with MT α -DG, compared to WT- α -DG as is revealed by MD simulations and hydrogen bond analysis. This indicates a likelihood of LCMV susceptibility when α -DG possesses T192M mutation. T192M mutation is a naturally occurring mutation in human causing structural changes of the protein and subsequently diminishing the effective signal transduction. Blocking the activity of this mutant form with small antagonists may anyway hamper the process. Gene therapies that deliver functional transcript of the protein may ameliorate the ill effect of the mutation. But from this study, we have found that LCMV GP1 has stronger interactions with the mutated form than the wild type one. That implies an effective

therapeutic strategy should be developed against the viral protein to block the interaction of LCMV GP1 with the host receptor protein. Studying the particular folding pattern (s) of LCMV GP1 in near future may lead the path to develop new potential therapeutic approaches to bar the spread of this viral transmission. The only licensed drug available to certain diseases caused by Arenaviruses is nucleoside analogue ribavirin [25]. A detailed analysis of this interaction with total protein model will generate deeper insight to the molecular basis of the viral attachment to mutant protein. Our future study therefore includes (i) homology modelling of total α -DG with its mutant form as well as that of LCMV GP1, (ii) docking simulations followed by thereafter analyses of the interactions and (iii) small molecular library screening to find effective molecule against the viral GP1.

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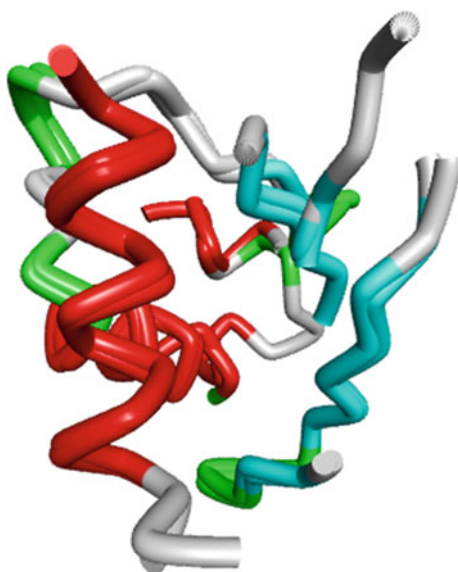
Conflict of Interest

The authors declare no conflict of interest.

Appendix

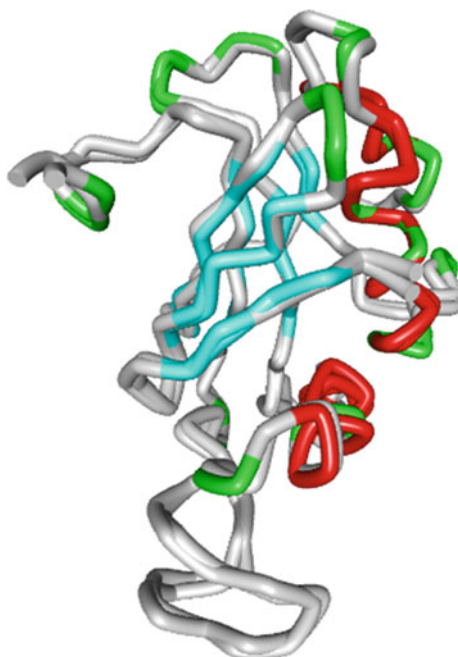
Supplementary

File 1 Superimposed models built from Modbase, RaptorX and I-TASSER

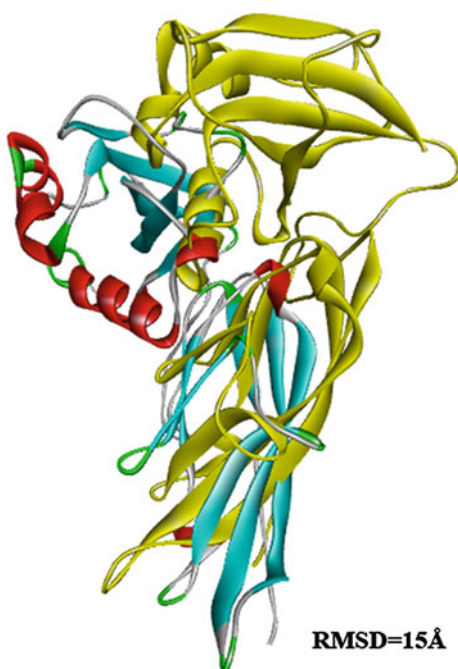


Supplementary

File 2 Superimposed
Reformed structure with its
original structure after heat
denaturation

**Supplementary**

File 3 Superimposed WT
and MT alpha-dystroglycan
minimized with explicit
solvent system



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