Computational and Molecular Dynamics Simulation Approach

To Analyze the Impact of *XPD* Gene Mutation on Protein Stability and Function

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Abstract

XPD acts as a functional helicase and aids in unwinding double helix around damaged DNA, leading to efficient DNA repair. Mutations of *XPD* give rise to DNA-repair deficiency diseases and cancer proneness. In this study, cancer-causing missense mutation that could inactivate helicase function and hinder its binding with other complexes were analysed using bioinformatics approach. Rigorous computational methods were employed to understand the molecular pathogenic profile of mutation. The mutant model with the desired mutation was built with I-TASSER. GROMACS 5.0.1 was used to evaluate the effect of a mutation on protein stability and function. Of the 276 missense mutations, 64 were found to be disease-causing. Out of these 64, seven were of cancer-causing mutations. Among these, we evaluated K48R mutation in a computational simulated environment to determine its impact on protein stability and function since K48 position was ascertained to be highly conserved and substitution with arginine could impair the *XPD* activity. Molecular Dynamic Simulation and Essential Dynamics analysis showed that K48R mutation altered protein structural stability and produced conformational drift. Our predictions thus revealed that K48R mutation could impair the *XPD* helicase activity and affect its ability to repair the damaged DNA, thus augmenting the risk for cancer.

Keywords: *XPD*; Nucleotide Excision Repair; Molecular Dynamics Simulation; Molecular Modelling; Cancer Promotion.

Introduction

The human *XPD* protein, encoded by *ERCC2* is a helicase with 5'–3' polarity [1]. It is a key component of the transcription-coupled nucleotide excision repair (NER) pathway that is critical for DNA damage repair and protects against gene mutations [2]. The crystal structure of *XPD* revealed the presence of two domains (HD1 and HD2) separated by a cleft containing the residues that bind ATP along with 4FeS cluster and Arch domain both of which inserted into the HD1 domain [3]. It is organized within the context of the general transcription factor IIIH (TFIIH) and has ATP-dependent helicase activity [4].

XPD assumes significance owing to its strikingly different roles during transcription and NER. *XPD* acts as a fully functional helicase by forming a core component of the transcription factor TFIIH during NER and aids in unwinding the DNA double helix around damaged DNA. Whereas in transcription, it acts as a scaffold for positioning additional factors like CAK complex [5].

Mutations of the human *XPD* gene is often associated with DNA repair deficiency and a high cancer proneness. It is reasonable that minor variations in the DNA repair mechanism owing to mutation may facilitate cancer development. To date almost 100 different mutations have been identified in the *XPD* gene [6,7]. Interestingly, most of the mutations affecting *XPD* are clustered in the C-terminal domain of the protein, which is the pivotal interaction domain of *XPD* for the p44 subunit of TFIIH [8]. Nonetheless, there is a dearth of literature that could distinguish the most significant mutation(s) responsible for cancer initiation and promotion.

Of late, computational analysis has been emerged as a credible approach to screen for deleterious mutation and ascertain the role of missense mutations on structural changes of a particular protein that would affect its activity. In this study, our objective was to evaluate the potential

effects of mutations residing at the different domains of *XPB* that could impair its function and play a role in cancer promotion. We primarily employed multiple computational algorithms such as, Meta-SNP, Pmut, and Provean to categorize deleterious mutations and later used FATHMM server to identify cancer-promoting/cancer-driving mutations among disease-causing mutations. Furthermore, we used mCSM, SDM2, STRUM, and Mutation Assessor to predict the impact of the mutation on protein structure and stability. A mutant model with desired missense mutation was built with I-TASSER server and a 3D mutated structure was simulated using GROMACS 5.0.1 to investigate the mechanism of structural consequences of mutation on *XPB* protein stability and function.

Materials and Methods

Collection of dataset

The mutations and associated information of *XPB* missense mutations were collected from HGMD (www.hgmd.cf.ac.uk/ac/index.php), COSMIC (<https://cancer.sanger.ac.uk/cosmic>), PubMed (<https://pubmed.ncbi.nlm.nih.gov/>). Sequence information in FASTA format was retrieved from UniProtKB (UniProt ID: P18074) (<https://www.uniprot.org/>) whereas structural information of *XPB* was obtained from Protein Data Bank (PDB ID: 5ivw) (<http://www.rcsb.org/>).

Computational pathogenicity analysis of mutations

Computational methods to understand the impact of mutations on proteins are important for classifying and prioritizing pathogenic and neutral single-nucleotide mutations.

Meta-SNP (<http://snps.biofold.org/meta-snp/>) incorporates the best-performing prediction algorithms to classify the deleteriousness of mutations in a protein. In addition to its algorithm, this method integrates a variety of other algorithms, including SNAP Prediction, PhD-SNP

Prediction, PANTHER Prediction, and SIFT Prediction. Meta-SNP is a 100-tree Random Forest WEKA library operation, trained on SV-2009 using 20-fold cross-validation. The predictor outputs the probability that a given mutation is disease-related, where scores >0.5 specify that the given mutation is disease-causing [9].

PMut (<http://mmb.irbbarcelona.org/PMut>) is a neural network-based program for the annotation of pathological mutations on proteins. It employs three parameters such as a mutation descriptors, solvent accessibility, and residue/sequence properties to estimate the pathogenicity indexes of given input mutation data with a prediction score between 0 and 1; mutations scoring from 0 to 0.5 are classified as neutral and those scoring from 0.5 to 1 are classified as pathological [10].

PROVEAN (Protein variation effect analyser - http://provean.jcvi.org/seq_submit.php) is a web server that uses an alignment-based score approach to predict whether an amino acid substitution or indel has an impact on the biological function of a protein [11]. Mutations are predicted as deleterious when the final scale is below the threshold value of -2.5 .

Mutation Assessor (<http://mutationassessor.org/r3/>) calculates the functional impact of amino acid substitutions in proteins. It is based on evolutionary conservation of the affected amino acid in protein homologs, specifying a rough estimate of a probability that the mutation has a phenotypic consequence at the level of an organism. It utilizes information based on the analysis of evolutionary conservation patterns in protein family multiple-sequence alignments. The analysis results in a functional impact score based on evolutionary information (FIS), variant conservation score (VC), and variant specificity score that classifies the mutations as neutral, low, medium or high [12].

Protein stability analysis

Studying the effects of mutation on protein stability and function is important in understanding its role in disease.

SDM2 (Site Directed Mutator -<http://marid.bioc.cam.ac.uk/sdm2>) is a computational method that analyses the variation of amino acid substitution occurring at a specific structural environment that is tolerated within the family of homologous proteins of known 3D structures and convert them into substitution probability tables which are used a quantitative measure for predicting the protein stability upon mutation [13].

mCSM (<http://biosig.unimelb.edu.au/mcsm/>) is a computational approach to predict the impact of missense mutation on protein stability and interactions between associating partners. This relies on graph-based signatures and encode distance patterns between atoms and is used to represent the protein residue environment and to train predictive models. mCSM evaluates the impact not only on protein stability but also on protein-protein and protein-nucleic acid interactions to understand the role of mutations in disease [14].

STRUM (<https://zhanglab.ccmb.med.umich.edu/STRUM/>) is a computational method for predicting stability changes ($\Delta\Delta G$) of a protein upon single-point mutation. It takes on a gradient boosting regression approach using a variety of features at different levels of evolutionary information and structural resolution [15].

DUET (<http://biosig.unimelb.edu.au/duet/>), is an integrated computational approach for predicting the effects of missense mutations on protein stability. DUET combines mCSM and SDM in a consensus prediction, by consolidating the results of the separate methods in an optimized predictor using Support Vector Machines (SVMs) trained with Sequential Minimal Optimization [16].

Cancer association analysis

FATHMM server (<http://fathmm.biocompute.org.uk/cancer.html>) was used to check the cancer association of the deleterious mutations. The server returns predictions capable of discriminating between cancer-promoting/cancer-driving mutation and other germline polymorphism. [17].

Analysis of sequence conservation

The ConSurf web server (<http://consurf.tau.ac.il>) analyses the evolutionary pattern of the amino acids of the protein to reveal regions that are important for structure and/or function. Starting from a query sequence or structure, the server automatically collects homologs, infers their multiple sequence alignment, and reconstructs a phylogenetic tree that reflects their evolutionary relations. These data are then used, within a probabilistic framework, to estimate the evolutionary rates of each sequence position [18].

Modeling mutation location on protein structure

The crystal structure of native *XPD* was downloaded from Protein data bank and was fixed using WHATIF server. The mutant model with desired mutation (K48R) was built using I-TASSER server [19] which uses multiple threading approach LOMETS with full-length atomic models constructed by iterative template-based fragment assembly simulations.

Quality assessment of Protein Model

A quality check of the mutant protein model which was obtained from I-TASSER server was performed using the Rampage server.

Molecular Dynamic (MD) Simulation

The best-scored mutant model structure obtained from I-TASSER was chosen as the starting coordinates for further analysis. To investigate the mechanism of structural consequences of the mutations on *XPD*, MD simulation of the K48R mutation was performed using GROMACS 5.0.1 [20] with OPLS force field where box type was cubic and size of the box was 2.5 – nm. The SPC water model was used and the system was neutralized by substituting a solvent molecule from Cl⁻ ions. A periodic boundary condition was applied in all directions. Subsequently a maximum of 50,000 steps of energy minimization was carried out for the predicted models using a conjugate gradient algorithm followed by steepest descent minimization. Then equilibration was carried out for 1000 ps for each system with NVT (constant number of particles, volume, and temperature) and the temperature was kept constant using a Berendsen thermostat followed by NPT (constant number of particles, pressure, and temperature) with Parinello-Rahman pressure coupling. Finally the equilibrated system was subjected to 25 ns MD simulation with time –step of 2 fs.

Analysis of MD trajectories

Comparative analysis of the Structural deviation in native and mutant (K48R) structure such as root mean square deviation (RMSD), root mean square fluctuation (RMSF), radius of gyration (Rg), solvent accessible surface area (SASA), Hydrogen bond, etc., were computed using GROMACS associated utility packages such as *g_rms*, *g_rmsf*, *g_gyrate*, *g_sas*, and *g_hbond*. GRACE software was used for plotting all graphs (<http://plasma-gate.weizmann.ac.il/Grace/>).

Secondary structure analysis

The software tool DSSP (Database of Secondary Structure in Proteins) by Kabsch and Sander was applied to analyse the change in secondary structure patterns in the native and mutant protein. DSSP tool employs H-bonding patterns and various other geometrical features to assign

secondary structure labels to the residues of a protein. Secondary structure pattern was plotted between native and mutant and superimposed at the beginning of the simulation and at specific time points where the conformational drifts occurred at a higher range.

Principal Component analysis

The principal component analysis is an unsupervised statistical technique for finding patterns in high-dimensional data. It is one of the effective methods for finding global and correlation motion by obtaining standard information from the MD trajectories through dimensionality reduction method. It has been used to distinguish the large scale collective motions from the random thermal fluctuations.

PCA method is based on the calculation and diagonalization of the covariance matrix. The elements C_{ij} in this matrix are defined by.

$$C_{ij} = (\bar{x}_i - \bar{x}) (\bar{x}_j - \bar{x})$$

Where $\bar{x}_i$ ($\bar{x}_j$) is the coordinate of the i th (j th) atom and represents an ensemble average. In general, the few initial principal components (PCs) are responsible for the most important conformational changes of the biomolecular system by storing eigenvectors with the highest eigenvalues. `g_covar` is GROMACS utility package that was used for generating the covariance matrix using the protein backbone as a reference structure for the rotational fit and `g_anaeig` was used to analyse and plot the eigenvectors.

Results

Our results illustrate the impact of missense mutations in the *XPD* gene on its protein structure, stability, and function. Deleterious or pathogenic spectrum, protein stability, and cancer-causing mutations were screened using advanced computational methods.

Dataset retrieval of missense mutations

We retrieved a list of 276 mutations from the public database of the *XPD* gene located at different coding regions for our investigation.

Analysis of disease-causing mutations

The pathogenic impact of missense mutations can be determined by evaluating the significance of the amino acids they affect. Summary of 276 missense mutations that were analysed by Meta-SNP (PATHER, PhD-SNP, SIFT, SNAP), Pmut, and Provean is represented as graph [Figure 1A] and detail dataset is presented as [Table1]. Results obtained from these servers showed that 67 mutations were predicted to be deleterious or disease-causing and were residing on different domains of *XPD* as illustrated in [Figure 1B].

Assessment of the functional impact of mutations

The mutation assessor predicted 57 mutations as high impacting on protein functionality out of 276 mutations screened [Table 2].

Protein stability analysis

mCSM, SDM, DUET, and STRUM were used to predict the impact of the mutation on protein stability. Different algorithms calculated varied results as illustrated in [Table 3]. mCSM predicted 245 mutations as destabilizing whereas SDM, DUET, and STRUM predicted 183, 212, and 68 mutations respectively as having the destabilizing effect on the protein.

Cancer-causing mutation analysis

A set of 64 mutations commonly identified by different algorithms was subjected to FATHMM server to determine mutations that could have a potential role in cancer-causing/cancer-promoting. Seven mutations such as G47R, K48R, R75I, R324H, D681N, R683Q, and R683W

were predicted to be cancer-causing/cancer-promoting [Table 4] and were residing on different domains of *XPD*.

Conservation analysis

Of the 7 cancer-causing mutations, K48R was taken for further comprehensive analysis and subjected to conservation analysis using the ConSurf server tool. The result obtained revealed that the K48 position was conserved at a scale of 6 [Figure 2]. Based on this analysis the K48R mutation was chosen for subsequent structural analysis in a computational simulated environment to determine its impact on protein stability and function.

Construction of a mutant model

Crystal structure with PDB id 5IVW was taken as a native control model for the analysis. For constructing the mutant model of K48R, a mutant sequence was submitted to I-TASSER server which first retrieved template protein of similar folds from the PDB library by locally installed Meta threading approach, where it generated ten thousand conformations (decoys). Then SPICKER program was used by I-TASSER to cluster all the decoys based on pairwise structure alignment and report up to five models that correspond to the five largest clusters. Model 1 with the best confidence score (C-score) [Supplementary Table 5] was taken for further analysis [Figure 3A, 3B].

Quality assessment of the model 1 was done using Ramachandran plot where 86.8% of the residues were found to be in the favoured region and analogous to Ramachandran plot derived for native XPD structure [Figure 4A, 4B].

Analysis of Molecular Dynamics Simulations

To apprehend the conformational changes in the XPD owing to K48R mutation, molecular dynamics simulation (MDS) was performed for 25 nanoseconds. Several parameters have been

analysed throughout the simulation trajectory including root mean square deviation (RMSD), root mean square fluctuations (RMSF), a total number of intramolecular hydrogen bonds, the radius of gyration, solvent accessible surface area (SASA) and secondary structure elements (SSE) of the protein with the time-dependent function of MDS.

RMSD profile for the backbone residue of the native and mutant protein was generated for all the atoms from the initial structure to understand the impact of the mutation on the stability of protein structure. [Figure 5A, 5B] shows that the RMSD value of the mutant structure is highly unstable as compared to the native protein. They showed a distinctly different type of deviation throughout the entire simulation, resulting in the backbone deviation range from ~0.4 nm (native) to ~1.0 nm (mutant) respectively. Native protein was found to be stabilized after 5 nanoseconds, whereas mutant protein lingered on till 15 nanoseconds to acquire stable conformation to a certain extent [Figure 5A, 5C].

Next, we analysed how mutant affected the dynamic behavior of the residue through the calculation of RMSF of the C α atom of the native and mutant protein. From [Figure 5D], it can be deduced that residue level fluctuations for mutant structure were rather high when compared with native structure, especially for residues located between 300 and 400 positions.

Subsequent intramolecular hydrogen bond analysis reaffirmed higher flexibility of mutant protein as we found a significant decrease in the number of hydrogen bond formation during the entire simulation as compared to the native structure [Figure 6C]. Native protein displayed the maximum number of hydrogen bonds in the range of 440 – 480 and whereas the number of hydrogen bonds drifted between 450 – 440 in the case of the mutant protein.

The radius of gyration (Rg) analysis revealed that mutant protein had the least compactness of its structure with 3.0 – 3.1 nm, while the native protein had shown to possess high compactness with 2.8 nm [Figure 6A].

The variation in SASA of mutant and native protein with time is depicted as [Figure 6B]. The native protein showed a lower SASA value in the range of $\sim 340 \text{ nm}^2$ – 360 nm^2 and remained consistent throughout the simulation period whereas the mutant form exhibited higher value in the range of ~ 425 – 470 nm^2 area with huge drift.

DSSP algorithm was applied to analyse the structural plasticity of protein. [Figure 7] showed the secondary structural elements as a function of simulation time. Coils, α -helix, turns, bends, and β -sheets were found in both native and mutant protein during the simulation time. However, the mutant protein showed a considerable decrease in α -helix forming residues with the concomitant increase in coils and bends forming residues as compared to native protein [Figure 7].

Essential dynamics (ED) analysis was performed to identify the correlated motions of the native and mutant protein which gives the sum of the eigenvalues measured for total motility of the system. The spectrum of eigenvalues indicated that major fluctuations of the system were confined to the first two eigenvectors of both native and mutant. Hence the projection of trajectories of native and mutant simulations in the phase space along the first two principal components (PC1, PC2) at 300 K was plotted and depicted as [Figure 8]. Mutant protein covered a larger region of phase space along PC1 and PC2 as compared to the native protein.

Discussion

XPD is a key NER enzyme that arbitrates in the transcription-coupled NER sub-pathway and can cause XP and other diseases when mutated in the germline [21]. However, recent advances in computational biology have afforded means to investigate genotype-phenotype correlation and

their association with disease status [22–26]. Several bioinformatics algorithms used in combination frequently spotlight candidate functional missense mutations associated with genes [27–31]. In this study, we employed various bioinformatics tools to screen potentially deleterious cancer-causing mutations of *XPD* that could have a profound impact on protein stability and function.

Several computational algorithms predicted 64 mutations as deleterious out of 276 mutations retrieved from the public database. Bioinformatics tools predicting protein stability upon mutation showed varied outputs. However, FATHMM analysis predicted 7 mutations as cancer-causing/cancer-promoting mutations. Among the seven mutations, we selected K48R mutation and performed conservation analysis which revealed that the K48 position was conserved at a scale of 6. A previous study investigating the impact of K48R mutation on XPD activity showed that it inhibits both ATPase and helicase activities and eventually impedes the opening of the damaged DNA for potential repair process [21,32–34]. Interestingly, this mutation lies in the HD1 domain and mainly resides in the ATP binding pocket of XPD [21], making it an alluring candidate for further comprehensive investigations to understand its impact on protein structure, stability, and functionality.

Effect of mutations on protein structure and function can be envisioned by identifying the locus point of mutated amino acid within the protein structure. Several studies have reported the impact of relationships between mutation and their location in protein structure [9,27]. The molecular modeling approach using I-TASSER to model the mutant protein and subsequent MDS analysis facilitated us to investigate the structural effect of this mutation on protein structure. RMSD data imply that distinctly different type of deviation was noticed in the mutant protein throughout the entire simulation period as against native protein, thereby clearly

demonstrating that mutation has a significant destabilizing effect on the protein. This was further corroborated by RMSF data which indicates that residue level variations were high for mutant protein, thereby indicating that mutation affected the protein conformation considerably leading to the increased flexibility of the protein. Subsequent intramolecular hydrogen bond analysis confirmed the higher flexibility of mutant protein as we found a significant decrease in the number of hydrogen bond formation during the entire simulation as compared to the native structure. Rg plot revealed the structural destabilizing effect on the protein owing to amino acid substitution at K48 that eventually leading to the loss of protein compactness. Besides, SASA analysis supported the Rg plot by returning higher values for mutant protein thus confirming the notion that protein might be enduring a major structural transition. Analysis of time-dependent secondary structure fluctuations through DSSP analysis showed a conformational drift from α -helix to coil form in mutant protein as the compared native protein. The conformational changes observed herein substantiate that major structural changes occurred due to amino acid substitution in the mutant structure which made it less stable, more flexible, and less compact. ED analysis demonstrated that the total motility of the mutant system was different from native protein and covered a larger region of phase space along PC1 and PC2 as compared to the native protein.

The association between the *in-silico* approach and wet lab experimentations has been rather evidenced by several previous studies [23,26]. Furthermore, computational mutation predictions when combined with MDS analysis has led to a breakthrough in the identification of most detrimental diseases causing mutations amid a huge pool of mutations [35]. Such computational approaches overlay the foundation for genetic studies to understand the molecular basis of

disease and subsequent remedial measures [23,24] for future assessments of genetic variants in the clinic.

Conclusion

Computational analysis of a large pool of missense mutations in the coding region of *XPB* revealed that substitution of lysine at 48th residue with arginine could be deleterious mutation with potential cancer-causing/cancer-promoting role. MDS and ED analysis showed its altered structural stability owing to an increase in flexibility and a decrease in compactness. It is conceivable that loss of structural integrity in mutant protein might lead to loss of its interaction with ATP as well as with other partner proteins that in turn could affect its ability to unwind the damaged DNA double helix. This could effectively diminish DNA repair process that eventually could increase the risk for cancer. The mechanistic insights from this study may provide a cue for wet lab me to ascertain the impact of K48R mutation on cancer formation and design appropriate therapeutic strategy.

Declaration of interest

The authors have no conflict of interest.

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Figure legends

Figure 1

Computational prediction and screening of mutation in XPD **A:** Screening of deleterious & neutral mutations using PATHER, PHD-SNP, SIFT, SNAP, Pmut, PROVEAN **B:** Deleterious mutations residing on different domains of XPD

Figure 2

Residue conservation analysis of K48th residue of XPD using ConSurf Server

Figure 3

3D mutant model **A:** 3D Mutant Model (K48R) by I-TASSER server **B:** Substitution of Arginine for Lysine at 48th residue of XPD

Figure 4

Quality Assessment of mutant and native models **A:** The Ramachandran plot analysis of mutant and native models **B:** Distribution of residues in Ramachandran plot.

Figure 5

Molecular dynamics simulation of native and mutant model protein at 25000 ps. **A:** Time evolution of backbone RMSD is shown as a function of time of the native and mutant structures at 25000 ps. Native is shown in green and mutant in red. **B:** Simulated K48R mutant after MD. **C:** Simulated Native after MD **D:** RMSF of the backbone C α atoms over the entire simulation. The ordinate is RMSF (nm) and the abscissa is an atom. Native is shown in green and mutant in red.

Figure 6

A: Radius of gyration of C α atoms of native and mutant structure versus time. Native is shown in green and mutant in red. **B:** Solvent-accessible surface area (SASA) of native and mutant structure versus time. Native is shown in green and mutant in red. **C:** Average number of

intermolecular hydrogen bonds in native and mutant structures as a function of time. Native is shown in green and mutant in red.

Figure 7

Time evolution of the secondary structural elements of a native and mutant structure at 25000 ps (DSSP classification)

Figure 8

2D Projection of Principal Component Analysis. Projection of the motion of the protein in phase space along the first two principal eigenvectors. Native is shown in green and mutant in red.

Table Legends

Table 1

Prediction of Deleterious Mutation using computational tools

Table 2

Prediction of Functional Impact using MutationAssessor Server

Table 3

Protein Stability prediction using computational servers

Table 4

Prediction Cancer association using FATHMM Server

Supplementary Table 1

C-score predicted using I-TASSER Server

A)

B)

Variable			Average			Conserved			
?	1	2	3	4	5	6	7	8	9

A)

B)

Native

K48R mutant

A. Ramachandran Plot

B. Distribution of Residues

Native

pico-seconds (ps)

Mutant

pico-seconds (ps)

2D projection of trajectory

Table 1:

Prediction of Deleterious Mutation using computational tools

Prediction of Deleterious Mutation															
Sr.no	Mutants	Meta-SNP										Pmut.		Provean	
		PANTHER		PhD-SNP		SIFT		SNAP		Meta-SNP					
		Prediction	Score	Prediction	Score	Prediction	Score	Prediction	Score	Prediction	Score	Prediction	Score	Prediction	Score
1	E20K	Neutral	0.427	Disease	0.821	Disease	0	Disease	0.655	Disease	0.756	Disease	0.64	Deleterious	-3.107
2	Q21E	Disease	0.978	Disease	0.84	Disease	0	Disease	0.71	Disease	0.799	Disease	0.78	Neutral	-2.33
3	S23F	Neutral	0.458	Disease	0.533	Disease	0.04	Neutral	0.485	Disease	0.51	Disease	0.54	Neutral	-2.229
4	M25L	Neutral	0.373	Disease	0.855	Disease	0.04	Neutral	0.525	Disease	0.572	Disease	0.52	Deleterious	-2.578
5	R26Q	Neutral	0.11	Neutral	0.23	Neutral	0.6	Neutral	0.125	Neutral	0.353	Neutral	0.15	Neutral	0.21
6	R26W	Neutral	0.446	Disease	0.534	Disease	0.02	Neutral	0.125	Neutral	0.353	Neutral	0.5	Neutral	-0.691
7	R30C	Disease	0.769	Disease	0.679	Disease	0	Disease	0.575	Disease	0.722	Disease	0.77	Deleterious	-5.371
8	T31M	Disease	0.709	Disease	0.596	Disease	0.01	Disease	0.565	Disease	0.707	Disease	0.83	Neutral	-2.37
9	H37R	Neutral	0.263	Disease	0.681	Disease	0	Disease	0.625	Disease	0.721	Disease	0.76	Deleterious	-6.515
10	V39I	Neutral	0.145	Neutral	0.084	Neutral	0.36	Neutral	0.215	Neutral	0.192	Neutral	0.28	Neutral	0.025
11	G47R	Disease	0.893	Disease	0.893	Disease	0	Disease	0.855	Disease	0.878	Disease	0.9	Deleterious	-7.219
12	K48R	Disease	0.511	Disease	0.7	Disease	0	Disease	0.81	Disease	0.774	Disease	0.9	Deleterious	-2.707
13	T49I	Disease	0.762	Disease	0.825	Disease	0.04	Disease	0.735	Disease	0.774	Disease	0.9	Deleterious	-5.414
14	L55P	Neutral	0.261	Disease	0.894	Disease	0.01	Disease	0.55	Disease	0.606	Disease	0.78	Deleterious	-6.317
15	M57K	Neutral	0.166	Disease	0.628	Disease	0.01	Disease	0.55	Disease	0.649	Neutral	0.26	Deleterious	-2.642
16	P64L	Neutral	0.446	Disease	0.863	Disease	0	Disease	0.57	Disease	0.739	Disease	0.68	Deleterious	-8.908
17	E66V	Neutral	0.101	Disease	0.726	Neutral	0.12	Disease	0.51	Disease	0.585	Disease	0.5	Neutral	-2.197
18	R75I	Disease	0.715	Disease	0.881	Disease	0	Disease	0.795	Disease	0.841	Disease	0.87	Deleterious	-7.303
19	T76A	Neutral	0.361	Disease	0.81	Disease	0.01	Disease	0.8	Disease	0.789	Disease	0.88	Deleterious	-4.564
20	P78S	Neutral	0.102	Neutral	0.105	Neutral	0.42	Neutral	0.34	Neutral	0.263	Neutral	0.29	Deleterious	-5.944
21	E86Q	Disease	0.772	Disease	0.806	Disease	0	Disease	0.64	Disease	0.576	Neutral	0.38	Deleterious	-2.755
22	R88G	Disease	0.594	Disease	0.695	Neutral	0.07	Disease	0.54	Disease	0.657	Disease	0.59	Deleterious	-4.462
23	N92S	Neutral	0.114	Neutral	0.103	Neutral	0.3	Neutral	0.19	Neutral	0.174	Neutral	0.25	Neutral	-0.181
24	F93L	Neutral	0.194	Neutral	0.441	Neutral	0.13	Neutral	0.47	Neutral	0.425	Neutral	0.35	Deleterious	-3.083
25	Y94S	Neutral	0.166	Neutral	0.487	Neutral	0.36	Disease	0.55	Neutral	0.444	Disease	0.59	Deleterious	-4.081
26	E95D	Neutral	0.243	Neutral	0.334	Neutral	0.38	Neutral	0.255	Neutral	0.419	Neutral	0.29	Neutral	-1.63
27	Q97L	Neutral	0.31	Neutral	0.253	Neutral	0.28	Neutral	0.38	Neutral	0.374	Disease	0.52	Deleterious	-4.035
28	E98D	Neutral	0.28	Neutral	0.253	Neutral	0.28	Neutral	0.38	Neutral	0.374	Neutral	0.14	Neutral	-0.321
29	K101T	Neutral	0.115	Neutral	0.331	Neutral	0.49	Neutral	0.265	Neutral	0.408	Neutral	0.34	Neutral	-0.878
30	P103L	Neutral	0.28	Neutral	0.259	Neutral	0.23	Neutral	0.41	Neutral	0.407	Neutral	0.49	Neutral	-1.998
31	P103R	Neutral	0.198	Neutral	0.278	Neutral	0.46	Neutral	0.385	Neutral	0.403	Neutral	0.34	Neutral	0.252
32	R112C	Disease	0.887	Disease	0.89	Disease	0	Disease	0.835	Disease	0.885	Disease	0.94	Deleterious	-7.231
33	R112G	Disease	0.691	Disease	0.844	Disease	0.04	Disease	0.79	Disease	0.82	Disease	0.92	Deleterious	-6.329
34	R112H	Disease	0.741	Disease	0.88	Disease	0	Disease	0.81	Disease	0.826	Disease	0.87	Deleterious	-4.526
35	H118R	Neutral	0.314	Disease	0.7	Disease	0	Disease	0.77	Disease	0.654	Disease	0.83	Deleterious	-5.333
36	P123T	Neutral	0.107	Neutral	0.143	Neutral	0.47	Neutral	0.22	Neutral	0.199	Neutral	0.16	Neutral	0.119
37	R125H	Neutral	0.206	Neutral	0.406	Disease	0.04	Disease	0.625	Neutral	0.452	Neutral	0.46	Deleterious	-3.104
38	D131N	Disease	0.504	Neutral	0.215	Disease	0	Disease	0.7	Neutral	0.315	Neutral	0.42	Deleterious	-4.576
39	C134T	Disease	0.611	Disease	0.942	Disease	0.03	Disease	0.815	Disease	0.866	Disease	0.82	Deleterious	-9.151
40	H135D	Neutral	0.219	Disease	0.667	Neutral	0.06	Disease	0.565	Disease	0.519	Disease	0.62	Deleterious	-3.182
41	S136N	Neutral	0.228	Neutral	0.309	Neutral	0.24	Neutral	0.395	Neutral	0.422	Neutral	0.38	Neutral	-0.321
42	Y141C	Disease	0.835	Disease	0.536	Neutral	0.17	Disease	0.525	Disease	0.63	Disease	0.61	Deleterious	-4.649
43	V142L	Neutral	0.26	Neutral	0.296	Neutral	0.71	Neutral	0.19	Neutral	0.412	Neutral	0.34	Neutral	-2.134
44	R143Q	Neutral	0.462	Disease	0.634	Neutral	0.53	Neutral	0.355	Neutral	0.496	Neutral	0.45	Deleterious	-3.193
45	R143G	Disease	0.705	Disease	0.736	Neutral	0.26	Disease	0.565	Disease	0.619	Neutral	0.39	Deleterious	-5.56
46	R143T	Disease	0.625	Disease	0.674	Neutral	0.43	Neutral	0.425	Disease	0.558	Disease	0.4	Deleterious	-4.592
47	A144V	Neutral	0.275	Neutral	0.292	Neutral	0.28	Neutral	0.28	Neutral	0.405	Neutral	0.33	Neutral	-1.552
48	H148T	Neutral	0.11	Neutral	0.319	Neutral	0.61	Neutral	0.31	Neutral	0.405	Neutral	0.09	Neutral	-0.419
49	D149N	Neutral	0.244	Neutral	0.388	Neutral	0.6	Neutral	0.32	Neutral	0.421	Neutral	0.27	Neutral	-1.454
51	L152R	Neutral	0.47	Disease	0.694	Neutral	0.45	Neutral	0.335	Disease	0.538	Disease	0.65	Deleterious	-2.984
52	Y158C	Disease	0.87	Disease	0.765	Neutral	0.17	Disease	0.555	Disease	0.734	Disease	0.55	Deleterious	-5.633
53	H164R	Neutral	0.11	Neutral	0.224	Neutral	0.37	Neutral	0.47	Neutral	0.362	Neutral	0.2	Neutral	-1.506
54	E167Q	Neutral	0.181	Neutral	0.293	Neutral	0.58	Neutral	0.225	Neutral	0.413	Neutral	0.25	Neutral	-1.383
55	V168M	Neutral	0.109	Neutral	0.154	Neutral	0.12	Neutral	0.23	Neutral	0.189	Neutral	0.24	Neutral	0.321
56	L170F	Disease	0.566	Neutral	0.463	Neutral	0.67	Neutral	0.22	Disease	0.574	Neutral	0.38	Deleterious	-2.731
57	L170R	Disease	0.857	Disease	0.879	Neutral	0.21	Disease	0.555	Disease	0.765	Neutral	0.48	Deleterious	-4.474
58	A172T	Neutral	0.166	Neutral	0.211	Neutral	0.49	Neutral	0.3	Neutral	0.311	Neutral	0.23	Neutral	0.034
59	N176S	Neutral	0.202	Neutral	0.189	Neutral	0.86	Neutral	0.285	Neutral	0.283	Neutral	0.25	Neutral	-0.756
60	D178E	Neutral	0.215	Neutral	0.216	Neutral	0.8	Neutral	0.25	Neutral	0.252	Neutral	0.3	Neutral	-1.006
60	G184V	Neutral	0.403	Disease	0.92	Disease	0	Disease	0.77	Disease	0.787	Disease	0.94	Deleterious	-6.724
61	R185T	Neutral	0.256	Neutral	0.465	Neutral	0.2	Disease	0.56	Neutral	0.456	Disease	0.65	Deleterious	-2.567
62	R186C	Disease	0.611	Disease	0.627	Disease	0.02	Disease	0.655	Disease	0.696	Disease	0.7	Deleterious	-3.395
63	R186H	Neutral	0.28	Neutral	0.347	Disease	0.05	Disease	0.58	Neutral	0.446	Neutral	0.39	Neutral	-1.529
64	Q187R	Neutral	0.184	Neutral	0.255	Neutral	0.42	Neutral	0.355	Neutral	0.36	Neutral	0.29	Neutral	0.539
65	S198L	Neutral	0.132	Neutral	0.435	Neutral	0.71	Neutral	0.22	Neutral	0.424	Neutral	0.49	Neutral	-0.027
66	I199M	Neutral	0.307	Neutral	0.351	Neutral	0.3	Neutral	0.43	Neutral	0.428	Neutral	0.35	Neutral	-1.543
67	H201T	Neutral	0.199	Neutral	0.402	Neutral	0.39	Disease	0.665	Neutral	0.437	Neutral	0.47	Deleterious	-4.156
68	A202V	Disease	0.517	Disease	0.883	Neutral	0.12	Neutral	0.49	Disease	0.594	Disease	0.68	Deleterious	-2.761
69	N203S	Neutral	0.276	Disease	0.713	Disease	0.05	Disease	0.615	Disease	0.724	Disease	0.66	Deleterious	-2.959
70	Y209C	Disease	0.923	Disease	0.952	Disease	0	Disease	0.84	Disease	0.901	Disease	0.94	Deleterious	-7.981
71	P215S	Neutral	0.481	Disease	0.715	Disease	0	Disease	0.62	Disease	0.583	Disease	0.43	Deleterious	-7.447
72	A218V	Neutral	0.434	Disease	0.72	Disease	0.03	Disease	0.605	Disease	0.719	Disease	0.84	Deleterious	-3.665
73	L220M	Neutral	0.329	Neutral	0.179	Neutral	0.21	Neutral	0.225	Neutral	0.271	Neutral	0.26	Neutral	-0.387
74	L220V	Neutral	0.132	Neutral	0.177	Neutral	0.7	Neutral	0.185	Neutral	0.227	Neutral	0.26	Neutral	-0.786
75	S222A	Neutral	0.352	Neutral	0.295	Disease	0.02	Disease	0.6	Neutral	0.154	Neutral	0.49	Deleterious	-2.793
76	A226T	NA	NA	Neutral	0.193	Neutral	0.52	Neutral	0.33	Neutral	0.154	Neutral	0.38	Neutral	0.078
77	R227C	Disease	0.773	Disease	0.587	Disease	0.01	Disease	0.595	Disease	0.726	Disease	0.78	Deleterious	-5.212
78	R227H	Neutral	0.445	Neutral	0.359	Disease	0.02	Disease	0.525	Neutral	0.456	Neutral	0.35	Deleterious	-3.164
79	K228T	Neutral	0.292	Neutral	0.256	Neutral	0.2	Neutral	0.455	Neutral	0.414	Neutral	0.41	Neutral	-1.235
80	A229V	Neutral	0.174	Neutral	0.361	Disease	0.03	Disease	0.6	Neutral	0.452	Disease	0.58	Deleterious	-2.626
81	V231M	Disease	0.611	Disease	0.713	Disease	0	Disease	0.7	Disease	0.726	Disease	0.84	Deleterious	-2.759

82	N241I	Disease	0.699	Disease	0.761	Neutral	0.08	Neutral	0.38	Disease	0.617	Disease	0.79	Deleterious	-8.528
83	I244M	Neutral	0.487	Neutral	0.404	Neutral	0.18	Neutral	0.285	Neutral	0.43	Disease	0.62	Deleterious	-2.701
84	I244T	Neutral	0.471	Disease	0.612	Disease	0.03	Disease	0.53	Neutral	0.495	Disease	0.63	Deleterious	-4.296
85	D245G	Neutral	0.414	Disease	0.792	Disease	0.05	Disease	0.575	Disease	0.73	Disease	0.68	Deleterious	-4.383
86	M247T	Neutral	0.312	Neutral	0.429	Disease	0.02	Disease	0.655	Neutral	0.472	Neutral	0.45	Deleterious	-4.632
87	N250S	Neutral	0.382	Neutral	0.251	Neutral	0.47	Neutral	0.345	Neutral	0.394	Neutral	0.29	Neutral	-0.376
88	T252P	Neutral	0.419	Disease	0.8	Neutral	0.19	Neutral	0.44	Disease	0.584	Neutral	0.48	Deleterious	-2.883
89	R253C	Disease	0.784	Disease	0.629	Disease	0.01	Disease	0.655	Disease	0.72	Disease	0.67	Deleterious	-5.828
90	R254G	Neutral	0.312	Neutral	0.438	Neutral	0.37	Disease	0.565	Neutral	0.47	Neutral	0.43	Deleterious	-4.004
91	R258T	Neutral	0.309	Neutral	0.336	Neutral	0.3	Neutral	0.49	Neutral	0.423	Disease	0.57	Neutral	-1.926
92	C259T	Neutral	0.2	Disease	0.549	Disease	0.01	Disease	0.67	Disease	0.657	Disease	0.66	Neutral	-1.831
93	K274E	Neutral	0.184	Disease	0.57	Disease	0.4	Disease	0.62	Neutral	0.469	Neutral	0.7	Deleterious	-3.464
94	Q279P	Neutral	0.299	Disease	0.687	Neutral	0.13	Disease	0.585	Disease	0.566	Neutral	0.33	Neutral	-2.453
95	R282Q	Neutral	0.103	Neutral	0.166	Neutral	1	Neutral	0.2	Neutral	0.177	Neutral	0.24	Neutral	0.139
96	D283V	Neutral	0.302	Neutral	0.431	Neutral	0.13	Neutral	0.42	Neutral	0.465	Disease	0.52	Deleterious	-3.85
97	R286T	Neutral	0.168	Neutral	0.29	Disease	0	Disease	0.635	Disease	0.726	Neutral	0.38	Neutral	-0.676
98	R287Y	Disease	0.644	Disease	0.602	Disease	0	Disease	0.635	Disease	0.726	Disease	0.65	Deleterious	-5.585
99	A297V	Neutral	0.104	Neutral	0.09	Neutral	0.29	Neutral	0.17	Neutral	0.149	Neutral	0.24	Neutral	-0.037
100	R299T	Neutral	0.191	Neutral	0.455	Neutral	0.17	Disease	0.56	Neutral	0.428	Neutral	0.44	Deleterious	-3.69
101	E300Q	Neutral	0.153	Neutral	0.307	Neutral	0.58	Neutral	0.24	Neutral	0.395	Neutral	0.32	Neutral	-1.652
102	T301K	Neutral	0.154	Neutral	0.527	Neutral	0.79	Neutral	0.41	Neutral	0.433	Neutral	0.34	Deleterious	-2.928
103	T301M	Neutral	0.476	Neutral	0.323	Neutral	0.09	Neutral	0.455	Neutral	0.402	Neutral	0.46	Deleterious	-3.565
104	N307K	Neutral	0.38	Disease	0.543	Neutral	0.05	Disease	0.565	Neutral	0.484	Disease	0.59	Deleterious	-5.093
105	D312Y	Neutral	0.499	Disease	0.65	Disease	0.01	Disease	0.73	Disease	0.731	Disease	0.55	Deleterious	-6.24
106	V314A	Disease	0.525	Neutral	0.227	Neutral	0.13	Disease	0.515	Neutral	0.155	Neutral	0.31	Deleterious	-3.413
107	Q316E	Neutral	0.184	Neutral	0.168	Neutral	0.36	Neutral	0.27	Neutral	0.173	Neutral	0.23	Neutral	-0.63
108	Q316K	Neutral	0.193	Neutral	0.144	Neutral	1	Neutral	0.205	Neutral	0.155	Neutral	0.25	Neutral	-0.369
109	I323M	Disease	0.616	Disease	0.586	Disease	0	Disease	0.72	Disease	0.617	Disease	0.42	Neutral	-2.307
110	R324H	Disease	0.792	Disease	0.762	Disease	0.01	Disease	0.655	Disease	0.688	Disease	0.53	Deleterious	-4.51
111	T325M	Neutral	0.375	Neutral	0.295	Disease	0.02	Disease	0.505	Neutral	0.429	Neutral	0.36	Neutral	-1.12
112	E327G	Neutral	0.46	Disease	0.755	Neutral	0.05	Disease	0.615	Disease	0.603	Disease	0.56	Deleterious	-5.175
113	R335W	Disease	0.84	Disease	0.924	Neutral	0.11	Neutral	0.305	Disease	0.511	Neutral	0.45	Deleterious	-7.217
114	R345H	Disease	0.524	Disease	0.618	Neutral	0.11	Neutral	0.305	Disease	0.751	Disease	0.42	Deleterious	-3.573
115	F394L	Disease	0.509	Disease	0.59	Neutral	0.31	Neutral	0.4	Disease	0.503	Disease	0.65	Deleterious	-4.418
116	P396L	Disease	0.526	Disease	0.668	Neutral	0.82	Neutral	0.41	Disease	0.541	Disease	0.55	Deleterious	-3.28
117	P396S	Neutral	0.115	Neutral	0.4	Neutral	0.72	Neutral	0.22	Neutral	0.414	Neutral	0.32	Neutral	-0.618
118	T398I	Neutral	0.372	Neutral	0.411	Neutral	0.29	Neutral	0.205	Neutral	0.451	Neutral	0.33	Neutral	-1.443
119	F403C	Disease	0.87	Disease	0.906	Disease	0	Disease	0.725	Disease	0.828	Disease	0.72	Deleterious	-6.957
120	F403S	Disease	0.748	Disease	0.892	Disease	0	Disease	0.69	Disease	0.746	Disease	0.72	Deleterious	-7.007
121	L406P	Disease	0.799	Disease	0.934	Disease	0	Disease	0.755	Disease	0.877	Disease	0.66	Deleterious	-6.675
122	V407I	Neutral	0.177	Neutral	0.359	Neutral	0.18	Neutral	0.29	Disease	0.428	Neutral	0.28	Neutral	-0.888
123	G413S	Disease	0.553	Disease	0.745	Disease	0.01	Disease	0.675	Disease	0.616	Neutral	0.39	Deleterious	-5.723
124	E419G	Disease	0.569	Disease	0.764	Disease	0.01	Disease	0.735	Disease	0.675	Disease	0.67	Deleterious	-6.624
125	E419K	Disease	0.577	Disease	0.783	Disease	0.02	Disease	0.76	Disease	0.649	Disease	0.66	Deleterious	-3.799
126	E419D	Neutral	0.221	Disease	0.513	Neutral	0.18	Neutral	0.375	Disease	0.463	Neutral	0.49	Deleterious	-2.841
127	D422H	Neutral	0.439	Disease	0.696	Disease	0.03	Disease	0.675	Disease	0.737	Neutral	0.4	Deleterious	-5.201
128	D423N	Neutral	0.295	Neutral	0.3	Neutral	0.43	Neutral	0.23	Neutral	0.422	Neutral	0.28	Neutral	-2.124
129	P426A	Neutral	0.085	Neutral	0.127	Neutral	0.91	Neutral	0.265	Neutral	0.167	Neutral	0.33	Deleterious	-4.291
130	P426S	Neutral	0.19	Neutral	0.243	Neutral	0.6	Neutral	0.255	Neutral	0.4	Neutral	0.36	Deleterious	-4.371
131	I428T	Neutral	0.195	Neutral	0.417	Neutral	0.2	Neutral	0.305	Neutral	0.444	Neutral	0.34	Deleterious	-2.857
132	A429V	Neutral	0.223	Neutral	0.365	Neutral	0.47	Neutral	0.385	Neutral	0.424	Neutral	0.3	Neutral	-0.605
133	M438T	Neutral	0.239	Disease	0.562	Disease	0	Disease	0.66	Disease	0.737	Disease	0.65	Deleterious	-4.063
134	D439N	Disease	0.574	Neutral	0.332	Disease	0	Disease	0.72	Disease	0.618	Neutral	0.37	Deleterious	-4.848
135	A440T	Neutral	0.35	Disease	0.551	Disease	0.03	Disease	0.58	Disease	0.642	Disease	0.76	Deleterious	-3.187
136	S441L	Disease	0.676	Disease	0.786	Disease	0.01	Disease	0.625	Disease	0.717	Disease	0.82	Deleterious	-5.584
137	I444V	Neutral	0.215	Neutral	0.264	Neutral	0.1	Neutral	0.25	Neutral	0.456	Neutral	0.65	Neutral	-0.691
138	V447I	Neutral	0.216	Neutral	0.162	Neutral	0.35	Neutral	0.215	Neutral	0.303	Neutral	0.33	Neutral	-0.533
139	R450C	NA	NA	Disease	0.631	Disease	0	Disease	0.675	Disease	0.732	Disease	0.72	Deleterious	-6.802
140	R450H	NA	NA	Neutral	0.41	Disease	0	Disease	0.615	Disease	0.334	Disease	0.65	Deleterious	-3.778
141	R450P	NA	NA	Disease	0.806	Disease	0	Disease	0.775	Disease	0.772	Disease	0.79	Deleterious	-5.848
142	F451L	Neutral	0.404	Neutral	0.499	Disease	0.01	Disease	0.67	Disease	0.508	Disease	0.76	Deleterious	-5.24
143	S453T	Neutral	0.322	Neutral	0.394	Neutral	0.15	Neutral	0.3	Neutral	0.469	Neutral	0.4	Neutral	-1.381
144	I455V	Neutral	0.292	Neutral	0.183	Neutral	0.52	Neutral	0.275	Neutral	0.254	Neutral	0.33	Neutral	-0.078
145	I456V	Neutral	0.292	Neutral	0.389	Neutral	0.06	Neutral	0.325	Neutral	0.462	Neutral	0.56	Neutral	-0.936
146	L461V	Neutral	0.388	Disease	0.685	Neutral	0.16	Disease	0.54	Disease	0.802	Disease	0.92	Neutral	-2.434
147	S462P	Disease	0.639	Disease	0.884	Disease	0	Disease	0.605	Disease	0.752	Disease	0.88	Deleterious	-4.903
148	D465A	Disease	0.544	Disease	0.537	Disease	0	Disease	0.675	Disease	0.553	Neutral	0.42	Deleterious	-6.512
149	D465T	Disease	0.613	Disease	0.512	Disease	0	Disease	0.67	Disease	0.675	Neutral	0.44	Deleterious	-5.748
150	I466S	Disease	0.634	Neutral	0.512	Disease	0	Disease	0.595	Disease	0.575	Disease	0.56	Deleterious	-2.548
151	P468L	Disease	0.565	Disease	0.611	Disease	0	Disease	0.645	Disease	0.684	Disease	0.58	Deleterious	-9.473
152	H474T	Neutral	0.11	Neutral	0.227	Neutral	0.63	Neutral	0.2	Neutral	0.399	Neutral	0.24	Neutral	-2.477
153	P475S	Neutral	0.295	Disease	0.59	Disease	0.03	Disease	0.6	Disease	0.502	Disease	0.43	Deleterious	-7.158
154	V476I	Neutral	0.423	Neutral	0.269	Neutral	0.1	Neutral	0.255	Neutral	0.468	Neutral	0.33	Neutral	-0.853
155	T477S	Neutral	0.203	Neutral	0.154	Neutral	0.09	Neutral	0.15	Neutral	0.302	Neutral	0.4	Neutral	-1.295
156	T480A	Neutral	0.146	Neutral	0.305	Disease	0.03	Neutral	0.36	Neutral	0.449	Neutral	0.33	Neutral	-0.681
157	M483I	Neutral	0.198	Neutral	0.375	Neutral	0.06	Neutral	0.455	Neutral	0.459	Disease	0.7	Deleterious	-3.456
158	M483T	Disease	0.66	Disease	0.593	Disease	0.01	Disease	0.74	Disease	0.759	Disease	0.9	Deleterious	-5.617
159	L485P	Disease	0.881	Disease	0.839	Disease	0.01	Disease	0.695	Disease	0.772	Disease	0.77	Deleterious	-6.865
160	A486T	Neutral	0.272	Neutral	0.325	Neutral	0.54	Neutral	0.15	Neutral	0.459	Neutral	0.45	Neutral	-1.098
161	R487W	Disease	0.924	Disease	0.76	Disease	0	Disease	0.805	Disease	0.861	Disease	0.86	Deleterious	-7.84
162	V488A	Neutral	0.105	Neutral	0.3	Neutral	0.46	Neutral	0.48	Neutral	0.437	Neutral	0.28	Neutral	0.758
163	C489S	Neutral	0.229	Neutral	0.413	Neutral	0.96	Disease	0.535	Neutral	0.465	Neutral	0.4	Deleterious	-6.633
164	M493L	Neutral	0.124	Neutral	0.243	Neutral	1	Neutral	0.44	Neutral	0.428	Neutral	0.4	Neutral	-0.656
165	I494F	Disease	0.669	Disease	0.804	Disease	0.04	Disease	0.585	Disease	0.635	Disease	0.57	Deleterious	-3.92
166	R497C	Disease	0.838	Disease	0.793	Disease	0.01	Disease	0.755	Disease	0.834	Disease	0.48	Deleterious	-6.613
167	R497S	Neutral	0.449	Disease	0.521	Disease	0.12	Disease	0.665	Disease	0.514	Disease	0.46	Deleterious	-4.444
168	R497I	Neutral	0.625	Disease	589	Disease	0.1	Disease	0.76	Disease	0.77	Disease	0.49	Deleterious	-6.58
169	Q501P	Disease	0.702	Disease	0.868	Neutral	0.08	Disease	0.665	Disease	0.514	Disease	0.74	Deleterious	-5.78
170	A503G	Neutral	0.381	Neutral	0.321	Neutral	0.32	Neutral	0.31	Neutral	0.46	Disease	0.55	Deleterious	-2.818
171	A503T	Neutral	0.193	Neutral	0.175	Neutral	0.35	Neutral	0.32	Neutral	0.307	Neutral	0.27	Neutral	-1.567
172	I504V	Neutral	0.2	Neutral	0.234	Neutral	0.59	Neutral	0.175	Neutral	0.437	Neutral	0.28	Neutral	-0.325
173	F508L	Neutral	0.35	Disease	0.743	Disease	0.1	Disease	0.665	Disease	0.668	Disease	0.84	Deleterious	-5.418

174	T510A	Neutral	0.173	Neutral	0.229	Neutral	0.52	Neutral	0.295	Neutral	0.426	Neutral	0.54	Neutral	-0.97
175	R511W	Disease	0.926	Disease	0.948	Disease	0	Disease	0.82	Disease	0.897	Disease	0.93	Deleterious	-7.707
176	D513V	NA	NA	Disease	0.797	Disease	0	Disease	0.645	Disease	0.734	Disease	0.61	Deleterious	-8.437
177	I514T	NA	NA	Neutral	0.384	Neutral	0.75	Neutral	0.320	Neutral	0.146	Neutral	0.33	Neutral	0.062
178	I517M	Neutral	0.494	Neutral	0.381	Neutral	0.07	Neutral	0.23	Neutral	0.414	Neutral	0.41	Neutral	-1.971
179	R518W	Disease	0.902	Disease	0.792	Disease	0	Disease	0.61	Disease	0.772	Disease	0.87	Deleterious	-7.54
180	L523F	Disease	0.517	Disease	0.598	Disease	0.01	Disease	0.555	Disease	0.513	Neutral	0.47	Deleterious	-3.32
181	V531F	Neutral	0.487	Disease	0.908	Disease	0	Disease	0.665	Disease	0.775	Disease	0.89	Deleterious	-4.467
182	V531I	Neutral	0	Neutral	0.303	Neutral	0.28	Neutral	0.29	Neutral	0.445	Neutral	0.49	Neutral	-0.813
183	G534D	Disease	0.557	Disease	0.946	Disease	0	Disease	0.77	Disease	0.89	Disease	0.94	Deleterious	-6.743
184	V536M	Disease	0.656	Disease	0.759	Disease	0	Disease	0.575	Disease	0.68	Disease	0.84	Deleterious	-2.819
185	F538S	Disease	0.834	Disease	0.952	Disease	0	Disease	0.7	Disease	0.85	Disease	0.94	Deleterious	-7.684
186	Y542C	Disease	0.943	Disease	0.944	Disease	0	Disease	0.83	Disease	0.897	Disease	0.94	Deleterious	-8.57
187	Q543P	Neutral	0.281	Disease	0.718	Neutral	0.32	Neutral	0.33	Disease	0.559	Neutral	0.31	Neutral	-1.45
188	M545L	Neutral	0.318	Disease	0.864	Disease	0.04	Disease	0.56	Disease	0.747	Disease	0.66	Neutral	-1.488
189	E546K	Disease	0.503	Disease	0.746	Neutral	0.1	Neutral	0.465	Disease	0.567	Neutral	0.45	Deleterious	-3.476
190	E546Q	Disease	0.52	Disease	0.578	Neutral	0.13	Neutral	0.210	Neutral	0.485	Neutral	0.46	Deleterious	-2.69
191	S547G	Neutral	0.252	Neutral	0.486	Neutral	0.4	Neutral	0.275	Neutral	0.448	Neutral	0.38	Neutral	-2.33
192	A550V	Disease	0.607	Neutral	0.413	Disease	0.05	Neutral	0.405	Disease	0.592	Neutral	0.47	Deleterious	-3.239
193	N564T	Neutral	0.203	Neutral	0.181	Neutral	0.1	Neutral	0.395	Neutral	0.322	Neutral	0.49	Deleterious	-2.755
194	I569F	Disease	0.634	Disease	0.511	Neutral	0.22	Neutral	0.255	Neutral	0.492	Neutral	0.61	Deleterious	-3.82
195	D573G	Neutral	0.275	Neutral	0.482	Disease	0.1	Disease	0.61	Neutral	0.5	Neutral	0.66	Deleterious	-6.539
196	V579I	Neutral	0.139	Neutral	0.035	Neutral	0.41	Neutral	0.08	Neutral	0.237	Neutral	0.23	Neutral	0.532
197	A580T	Disease	0.545	Neutral	0.229	Disease	0.03	Disease	0.54	Disease	0.503	Disease	0.76	Deleterious	-3.853
198	L581P	Disease	0.881	Disease	0.863	Neutral	0.09	Disease	0.635	Disease	0.781	Disease	0.87	Deleterious	-6.677
199	E586V	Neutral	0.359	Neutral	0.371	Disease	0.04	Disease	0.51	Neutral	0.489	Neutral	0.61	Deleterious	-3.668
200	C588F	Disease	0.881	Disease	0.881	Disease	0.03	Disease	0.615	Disease	0.808	Disease	0.9	Deleterious	-9.698
201	E589K	Neutral	0.256	Neutral	0.31	Neutral	0.08	Neutral	0.3	Neutral	0.458	Neutral	0.39	Deleterious	-2.902
202	R592C	Disease	0.631	Disease	0.832	Disease	0	Disease	0.67	Disease	0.765	Disease	0.92	Deleterious	-7.518
203	R592H	Disease	0.715	Disease	0.64	Disease	0.03	Disease	0.665	Disease	0.683	Disease	0.76	Deleterious	-4.694
204	R592P	Disease	0.715	Disease	0.925	Disease	0.01	Disease	0.735	Disease	0.817	Disease	0.76	Deleterious	-6.532
205	G593R	Disease	0.568	Disease	0.924	Disease	0.01	Disease	0.67	Disease	0.765	Disease	0.88	Deleterious	-7.618
206	I595M	Disease	0.55	Disease	0.517	Neutral	0.08	Neutral	0.2	Neutral	0.49	Neutral	0.39	Neutral	-1.964
207	G602D	Neutral	0.299	Disease	0.962	Disease	0	Disease	0.855	Disease	0.914	Disease	0.94	Deleterious	-6.661
208	G607A	Disease	0.788	Disease	0.912	Disease	0	Disease	0.64	Disease	0.751	Disease	0.88	Deleterious	-5.713
209	I608M	Disease	0.65	Disease	0.762	Disease	0.02	Neutral	0.405	Disease	0.606	Disease	0.79	Neutral	-2.354
210	V611A	Neutral	0.137	Neutral	0.223	Neutral	0.08	Neutral	0.25	Neutral	0.39	Neutral	0.23	Neutral	0.929
211	R616C	Disease	0.922	Disease	0.967	Disease	0	Disease	0.81	Disease	0.909	Disease	0.94	Deleterious	-7.518
212	R616P	Disease	0.806	Disease	0.973	Disease	0	Disease	0.8	Disease	0.915	Disease	0.94	Deleterious	-6.532
213	R616Q	Disease	0.531	Disease	0.946	Disease	0	Disease	0.755	Disease	0.885	Disease	0.94	Deleterious	-3.709
214	R616W	Disease	0.93	Disease	0.973	Disease	0	Disease	0.805	Disease	0.894	Disease	0.89	Deleterious	-7.518
215	V618I	Neutral	0.404	Disease	0.797	Disease	0.02	Neutral	0.49	Disease	0.57	Disease	0.76	Neutral	-0.952
216	I619V	Neutral	0.212	Neutral	0.446	Neutral	0.52	Neutral	0.165	Neutral	0.464	Neutral	0.33	Neutral	-0.751
217	G622V	Disease	0.903	Disease	0.976	Disease	0	Disease	0.72	Disease	0.841	Disease	0.94	Deleterious	-8.526
218	V623I	Neutral	0.102	Neutral	0.136	Neutral	0.71	Neutral	0.15	Neutral	0.27	Neutral	0.31	Neutral	0.288
219	V626I	Neutral	0.175	Neutral	0.396	Neutral	0.43	Neutral	0.22	Neutral	0.454	Neutral	0.47	Neutral	-0.819
220	T628I	Neutral	0.422	Neutral	0.482	Disease	0.03	Disease	0.56	Neutral	0.492	Disease	0.71	Deleterious	-5.71
221	Q629H	Neutral	0.371	Neutral	0.409	Neutral	0.12	Neutral	0.235	Neutral	0.462	Neutral	0.25	Deleterious	-3.281
222	R631H	Disease	0.706	Disease	0.612	Neutral	0.06	Neutral	0.29	Disease	0.521	Disease	0.57	Deleterious	-4.557
223	R631L	Disease	0.7	Disease	0.805	Neutral	0.2	Neutral	0.49	Disease	0.639	Disease	0.59	Deleterious	-6.383
224	R631P	Disease	0.801	Disease	0.654	Neutral	0.21	Disease	0.565	Disease	0.589	Disease	0.51	Deleterious	-6.284
225	I632C	Disease	0.827	Disease	0.742	Disease	0.02	Disease	0.52	Disease	0.645	Disease	0.92	Deleterious	-4.399
226	K634E	Neutral	0.423	Disease	0.585	Neutral	0.08	Neutral	0.305	Neutral	0.49	Neutral	0.62	Deleterious	-2.927
227	A635V	Disease	0.622	Disease	0.624	Disease	0.01	Disease	0.545	Disease	0.653	Disease	0.72	Deleterious	-3.762
228	R647L	Disease	0.522	Disease	0.699	Neutral	0.24	Disease	0.525	Disease	0.613	Disease	0.61	Deleterious	-5.51
229	F654L	Neutral	0.311	Neutral	0.474	Neutral	0.12	Disease	0.585	Disease	0.836	Neutral	0.4	Deleterious	-5.463
230	R658H	Disease	0.87	Disease	0.88	Disease	0.02	Disease	0.69	Disease	0.808	Disease	0.61	Deleterious	-4.563
231	R658G	Disease	0.831	Disease	0.908	Disease	0.02	Disease	0.705	Disease	0.791	Disease	0.85	Deleterious	-6.38
232	H659Y	Disease	0.589	Disease	0.785	Neutral	0.34	Neutral	0.245	Disease	0.683	Disease	0.84	Deleterious	-4.304
233	A660S	Neutral	0.454	Disease	0.721	Neutral	0.06	Neutral	0.415	Disease	0.548	Disease	0.57	Neutral	-1.938
234	C663R	Disease	0.793	Disease	0.934	Disease	0.02	Disease	0.765	Disease	0.871	Disease	0.91	Deleterious	-11.243
235	R666Q	Disease	0.772	Disease	0.935	Disease	0	Disease	0.84	Disease	0.903	Disease	0.94	Deleterious	-3.737
236	R666W	Disease	0.959	Disease	0.956	Disease	0	Disease	0.84	Disease	0.901	Disease	0.94	Deleterious	-7.474
237	T672A	Neutral	0.158	Neutral	0.473	Neutral	0.63	Neutral	0.37	Neutral	0.431	Neutral	0.54	Neutral	-2.488
238	T672M	Neutral	0.482	Disease	0.506	Neutral	0.06	Neutral	0.26	Neutral	0.496	Neutral	0.63	Deleterious	-3.787
239	G675S	Disease	0.808	Disease	0.805	Disease	0.01	Disease	0.615	Disease	0.664	Disease	0.76	Deleterious	-5.609
240	M677I	Disease	0.503	Neutral	0.254	Neutral	0.11	Neutral	0.315	Neutral	0.225	Neutral	0.46	Deleterious	-3.74
241	M677V	Neutral	0.481	Disease	0.587	Neutral	0.18	Neutral	0.35	Neutral	0.493	Neutral	0.48	Deleterious	-3.74
242	M677T	Disease	0.55	Disease	0.75	Disease	0.02	Disease	0.515	Disease	0.656	Disease	0.77	Deleterious	-5.609
243	V678A	Disease	0.523	Disease	0.592	Disease	0.04	Disease	0.533	Disease	0.641	Disease	0.92	Deleterious	-3.488
244	D681N	Disease	0.738	Disease	0.94	Disease	0	Disease	0.83	Disease	0.928	Disease	0.93	Deleterious	-4.674
245	K682T	Neutral	0.358	Neutral	0.361	Disease	0.03	Disease	0.6	Neutral	0.499	Neutral	0.7	Deleterious	-5.464
246	R683Q	Disease	0.772	Disease	0.919	Disease	0	Disease	0.865	Disease	0.866	Disease	0.94	Deleterious	-3.662
247	R683W	Disease	0.959	Disease	0.945	Disease	0	Disease	0.865	Disease	0.897	Disease	0.94	Deleterious	-7.312
248	F684C	Disease	0.733	Disease	0.921	Disease	0	Disease	0.67	Disease	0.772	Disease	0.83	Deleterious	-6.418
249	F684L	Neutral	0.325	Disease	0.831	Disease	0.01	Neutral	0.485	Disease	0.599	Disease	0.61	Deleterious	-4.865
250	R686H	Disease	0.578	Neutral	0.404	Disease	0.01	Disease	0.535	Disease	0.623	Neutral	0.38	Deleterious	-4.348
251	R686C	Disease	0.812	Disease	0.673	Disease	0	Disease	0.63	Disease	0.73	Disease	0.5	Deleterious	-6.97
252	R686P	Disease	0.651	Disease	0.834	Disease	0.01	Disease	0.615	Disease	0.775	Disease	0.78	Deleterious	-6.041
253	R690P	Disease	0.719	Disease	0.855	Disease	0	Disease	0.795	Disease	0.821	Disease	0.71	Deleterious	-5.529
254	R690Q	Neutral	0.435	Neutral	0.31	Disease	0.03	Disease	0.605	Neutral	0.499	Neutral	0.39	Deleterious	-3.042
255	R690W	Disease	0.891	Disease	0.741	Disease	0	Disease	0.71	Disease	0.785	Disease	0.52	Deleterious	-6.665
256	K692N	Disease	0.597	Disease	0.578	Disease	0	Disease	0.685	Disease	0.538	Neutral	0.43	Deleterious	-4.539
257	P694S	Disease	0.748	Neutral	0.284	Neutral	0.11	Neutral	0.415	Disease	0.509	Neutral	0.43	Deleterious	-7.379
258	R695H	Neutral	0.303	Neutral	0.265	Neutral	0.09	Neutral	0.4	Neutral	0.447	Neutral	0.38	Deleterious	-2.766
259	R695P	Neutral	0.134	Disease	0.723	Neutral	0.27	Neutral	0.45	Disease	0.574	Neutral	0.49	Deleterious	-3.371
260	R695S	Neutral	0.168	Neutral	0.237	Neutral	0.08	Neutral	0.465	Neutral	0.437	Neutral	0.32	Neutral	-2.258
261	H700Y	Neutral	0.159	Neutral	0.306	Neutral	1	Neutral	0.26	Neutral	0.454	Neutral	0.34	Neutral	0.776
262	T702I	Neutral	0.278	Neutral	0.306	Neutral	0.21	Neutral	0.33	Neutral	0.415	Neutral	0.4	Deleterious	-3.175
263	A704V	Neutral	0.32	Neutral	0.297	Disease	0.04	Disease	0.55	Neutral	0.429	Neutral	0.31	Neutral	-2.299
264	N705D	Neutral	0.182	Neutral	0.274	Neutral	0.69	Neutral	0.23	Neutral	0.404	Neutral	0.28	Neutral	-1.324
265	N705I	Neutral	0.258	Disease	0.588	Neutral	0.4	Neutral	0.395	Disease	0.534	Disease	0.56	Neutral	-0.209
266	N705S	Neutral	0.171	Neutral	0.287	Neutral	0.87	Neutral	0.23	Neutral	0.404	Neutral	0.2		

267	N707T	Disease	0.687	Disease	0.681	Neutral	0.19	Neutral	0.395	Disease	0.561	Disease	0.56	Deleterious	-5.097
268	T709I	Disease	0.508	Disease	0.515	Neutral	0.11	Neutral	0.445	Neutral	0.488	Neutral	0.44	Deleterious	-3.048
269	V710M	Neutral	0.48	Disease	0.824	Disease	0.02	Disease	0.53	Disease	0.608	Neutral	0.49	Neutral	-1.366
270	D711N	Neutral	0.345	Disease	0.789	Disease	0.04	Neutral	0.455	Disease	0.578	Neutral	0.43	Deleterious	-3.574
271	D711Y	Disease	0.748	Disease	0.922	Disease	0	Disease	0.67	Disease	0.77	Disease	0.61	Deleterious	-6.481
272	G713R	Disease	0.504	Disease	0.793	Disease	0.01	Disease	0.695	Disease	0.789	Disease	0.67	Neutral	-1.204
273	A717G	Neutral	0.428	Disease	0.631	Neutral	0.08	Disease	0.54	Disease	0.336	Disease	0.71	Neutral	-2.489
274	R722P	Disease	0.573	Disease	0.919	Neutral	0.2	Disease	0.72	Disease	0.777	Disease	0.79	Deleterious	-5.422
275	M724T	Disease	0.684	Disease	0.823	Disease	0.01	Disease	0.765	Disease	0.781	Disease	0.81	Deleterious	-5.151
276	A725P	Disease	0.623	Disease	0.867	Disease	0.04	Disease	0.73	Disease	0.669	Disease	0.55	Deleterious	-4.097

Table 2:

Prediction of Functional Impact using MutationAssessor Server

Sr.no	Mutants	MutationAssessor Prediction			
		FI score	VC score	VS score	Functional Impact
1	E20K	3.785	4.57	3	high
2	Q21E	3.855	4.71	3	high
3	S23F	2.865	3.43	2.3	medium
4	M25L	3.69	4.24	3.14	high
5	R26Q	1.63	3.26	0	low
6	R26W	0.185	1.06	-0.69	neutral
7	R30C	3.525	4.16	2.89	high
8	T31M	3.265	4.23	2.3	medium
9	H37R	3.61	4.08	3.14	high
10	V39I	1.265	0.13	2.4	low
11	G47R	3.97	4.8	3.14	high
12	K48R	4.315	5.49	3.14	high
13	T49I	4.25	5.36	3.14	high
14	L55P	3.17	3.25	3.09	medium
15	M57K	1.04	1.39	0.69	low
16	P64L	3.19	3.24	3.14	medium
17	E66V	2.005	2.62	1.39	medium
18	R75I	4.46	5.62	3.3	high
19	T76A	4.46	5.62	3.3	high
20	P78S	1.225	-0.81	3.26	low
21	E86Q	3.265	3.27	3.26	medium
22	R88G	2.73	2.9	2.56	medium
23	N92S	0.55	0	1.1	neutral
24	F93L	0.77	1.13	0.41	neutral
25	Y94S	2.61	2.22	3	medium
26	E95D	2.175	1.41	2.94	medium
27	Q97L	1.195	1.14	1.25	low
28	E98D	-0.39	0.32	-1.1	neutral
29	K101T	1.085	1.07	1.1	low
30	P103L	1.83	2.97	0.69	low
31	P103R	0.61	0.53	0.69	neutral
32	R112C	4.44	5.62	3.26	high
33	R112G	4.44	5.62	3.26	high
34	R112H	4.44	5.62	3.26	high
35	H118R	3.35	3.81	2.89	medium
36	P123T	-0.185	-0.37	0	neutral
37	R125H	2.72	2.26	3.18	medium
38	D131N	1.88	0.5	3.26	low
39	C134T	NA	NA	NA	NA
40	H135D	1.91	1.42	2.4	low
41	S136N	1.785	1.27	2.3	low
42	Y141C	2.31	2.14	2.48	medium
43	V142L	2.22	1.61	2.83	medium
44	R143Q	3.3	3.38	3.22	medium
45	R143G	3.3	3.38	3.22	medium
46	R143T	NA	NA	NA	NA
47	A144V	2.04	2	2.08	medium
48	H148T	NA	NA	NA	NA
49	D149N	1.135	0.93	1.34	low
51	L152R	1.735	2.08	1.39	low
52	Y158C	3.405	4.04	2.77	medium
53	H164R	0.76	-0.09	1.61	neutral
54	E167Q	0.85	0.6	1.1	low
55	V168M	1.655	1.7	1.61	low
56	L170F	2.365	1.79	2.94	medium
57	L170R	3.145	3.35	2.94	medium
58	A172T	0.94	1.37	0.51	low
59	N176S	0.17	-0.41	0.75	neutral
60	D178E	0.255	-1.48	1.99	neutral
60	G184V	4.365	5.47	3.26	high
61	R185T	NA	NA	NA	NA
62	R186C	2.675	3.74	1.61	medium
63	R186H	2.125	2.64	1.61	medium
64	Q187R	-0.985	-0.77	-1.2	neutral
65	S198L	-0.375	-1.44	0.69	neutral
66	I199M	1.605	0.91	2.3	low
67	H201T	NA	NA	NA	NA
68	A202V	2.92	2.54	3.3	medium
69	N203S	2.22	2.3	2.14	medium
70	Y209C	4.47	5.61	3.33	high
71	P215S	3.115	2.9	3.33	medium
72	A218V	3.86	4.39	3.33	high
73	L220M	2.135	1.44	2.83	medium
74	L220V	0.665	0.69	0.64	neutral
75	S222A	3.27	3.24	3.3	medium
76	A226T	0.64	0.94	0.34	neutral
77	R227C	2.98	3.4	2.56	medium
78	R227H	2.98	3.4	2.56	medium
79	K228T	1.065	1.03	1.1	low
80	A229V	2.595	3.24	1.95	medium
81	V231M	4.315	5.3	3.33	high
82	N241I	3.92	4.58	3.26	high
83	I244M	3.645	4.03	3.26	high
84	I244T	3.445	3.63	3.26	medium

85	D245G	3.455	4.2	2.71	medium
86	M247T	2.43	1.72	3.14	medium
87	N250S	0.295	0.08	0.51	neutral
88	T252P	2.42	2.36	2.48	medium
89	R253C	3.37	3.91	2.83	medium
90	R254G	3.005	3.07	2.94	medium
91	R258T	NA	NA	NA	NA
92	C259T	NA	NA	NA	NA
93	K274E	2.485	3.36	1.61	medium
94	Q279P	2.02	2.94	1.1	medium
95	R282Q	-0.56	-1.12	0	neutral
96	D283V	1.775	2.86	0.69	low
97	R286T	NA	NA	NA	NA
98	R287Y	NA	NA	NA	NA
99	A297V	-0.32	-0.64	0	neutral
100	R299T	NA	NA	NA	NA
101	E300Q	1.245	1.1	1.39	low
102	T301K	2.125	2.64	1.61	medium
103	T301M	2.47	3.33	1.61	medium
104	N307K	2.68	3.75	1.61	medium
105	D312Y	2.8	3.99	1.61	medium
106	V314A	2.01	3.33	0.69	medium
107	Q316E	1.355	1.1	1.61	low
108	Q316K	0.645	-0.32	1.61	neutral
109	I323M	2.8	3.99	1.61	medium
110	R324H	3.175	4.74	1.61	medium
111	T325M	1.545	2.4	0.69	low
112	E327G	2.985	4.58	1.39	medium
113	R335W	3.115	4.62	1.61	medium
114	R345H	2.8	3.99	1.61	medium
115	F394L	1.34	2.27	0.41	low
116	P396L	2.485	3.58	1.39	medium
117	P396S	0.965	0.54	1.39	low
118	T398I	1.01	0.92	1.1	low
119	F403C	3.125	4.64	1.61	medium
120	F403S	3.125	4.64	1.61	medium
121	L406P	3.16	4.71	1.61	medium
122	V407I	1.74	1.87	1.61	low
123	G413S	3.175	4.74	1.61	medium
124	E419G	3.64	4.51	2.77	high
125	E419K	3.64	4.51	2.77	high
126	E419D	2.49	2.21	2.77	medium
127	D422H	3.16	3.76	2.56	medium
128	D423N	1.81	1.61	2.01	low
129	P426A	1.555	0.34	2.77	low
130	P426S	2.155	1.54	2.77	medium
131	I428T	2.27	2.34	2.2	medium
132	A429V	1.1	1.1	1.1	low
133	M438T	2.67	3.04	2.3	medium
134	D439N	3.34	3.91	2.77	medium
135	A440T	3.22	4.36	2.08	medium
136	S441L	3.24	3.77	2.71	medium
137	I444V	2.25	2.8	1.7	medium
138	V447I	1.445	1.35	1.54	low
139	R450C	3.52	4.33	2.71	high
140	R450H	2.825	3.64	2.01	medium
141	R450P	3.52	4.33	2.71	high
142	F451L	3.58	4.45	2.71	high
143	S453T	1.33	1.78	0.88	low
144	I455V	0.015	0.39	-0.36	neutral
145	I456V	2.825	2.94	2.71	medium
146	L461V	3.435	4.16	2.71	medium
147	S462P	3.675	4.58	2.77	high
148	D465A	3.465	4.16	2.77	medium
149	D465T	NA	NA	NA	NA
150	I466S	2.05	2.71	1.39	medium
151	P468L	3.665	4.56	2.77	high
152	H474T	NA	NA	NA	NA
153	P475S	3.15	3.53	2.77	medium
154	V476I	2.74	2.77	2.71	medium
155	T477S	0.6	0.69	0.51	neutral
156	T480A	0.785	0.18	1.39	neutral
157	M483I	1.99	2.44	1.54	medium
158	M483T	3.58	4.52	2.64	high
159	L485P	3.63	4.49	2.77	high
160	A486T	1.69	0.67	2.71	low
161	R487W	3.685	4.6	2.77	high
162	V488A	1.1	1.1	1.1	low
163	C489S	0.975	0.77	1.18	low
164	M493L	0.78	0.17	1.39	neutral
165	I494F	3.055	3.47	2.64	medium
166	R497C	2.9	3.5	2.3	medium
167	R497S	3.245	4.19	2.3	medium
168	R497I	NA	NA	NA	NA
169	Q501P	3.605	4.5	2.71	high
170	A503G	2.66	3.02	2.3	medium
171	A503T	1.23	1.77	0.69	low
172	I504V	1.48	0.76	2.2	low
173	F508L	3.48	4.48	2.48	medium
174	T510A	1.59	0.88	2.3	low
175	R511W	3.66	4.61	2.71	high
176	D513V	3.63	4.49	2.77	high
177	I514T	-0.4	-0.29	-0.51	neutral
178	I517M	1.605	2.01	1.2	low

179	R518W	3.59	4.47	2.71	high
180	L523F	3.165	3.69	2.64	medium
181	V531F	4.2	5.36	3.04	high
182	V531I	1.44	0.93	1.95	low
183	G534D	4.615	5.83	3.4	high
184	V536M	4.3	5.27	3.33	high
185	F538S	4.61	5.82	3.4	high
186	Y542C	4.6	5.77	3.43	high
187	Q543P	-0.265	-0.53	0	neutral
188	M545L	0.475	-0.11	1.06	neutral
189	E546K	2.2	1.73	2.67	medium
190	E546Q	2.5	1.63	3.37	medium
191	S547G	2.215	2.08	2.35	medium
192	A550V	2.69	3.08	2.3	medium
193	N564T	1.86	1.32	2.4	low
194	I569F	1.9	1.24	2.56	low
195	D573G	2.03	0.66	3.4	medium
196	V579I	-0.17	0	-0.34	neutral
197	A580T	2.325	1.22	3.43	medium
198	L581P	4.43	5.46	3.4	high
199	E586V	2.39	2.83	1.95	medium
200	C588F	3.955	4.48	3.43	high
201	E589K	1.095	0.24	1.95	low
202	R592C	3.315	3.26	3.37	medium
203	R592H	3.2	3.03	3.37	medium
204	R592P	3.315	3.26	3.37	medium
205	G593R	4.645	5.82	3.47	high
206	I595M	2.21	2.02	2.4	medium
207	G602D	4.265	5.1	3.43	high
208	G607A	4.29	5.15	3.43	high
209	I608M	3.13	3.86	2.4	medium
210	V611A	-1.115	-3.33	1.1	neutral
211	R616C	4.635	5.84	3.43	high
212	R616P	4.635	5.84	3.43	high
213	R616Q	4.285	5.14	3.43	high
214	R616W	4.635	5.84	3.43	high
215	V618I	3.04	2.65	3.43	medium
216	I619V	0.825	0.04	1.61	low
217	G622V	4.65	5.83	3.47	high
218	V623I	-0.58	-0.83	-0.33	neutral
219	V626I	1.44	1.56	1.32	low
220	T628I	1.755	0.04	3.47	low
221	Q629H	1.425	0.37	2.48	low
222	R631H	2.445	1.52	3.37	medium
223	R631L	1.815	0.96	2.67	low
224	R631P	1.415	-0.54	3.37	low
225	I632C	NA	NA	NA	NA
226	K634E	3.12	3.15	3.09	medium
227	A635V	2.25	1.79	2.71	medium
228	R647L	2.14	1.34	2.94	medium
229	F654L	2.22	1.01	3.43	medium
230	R658H	3.565	3.76	3.37	high
231	R658G	4.46	5.55	3.37	high
232	H659Y	3.22	3.3	3.14	medium
233	A660S	2.43	2.42	2.44	medium
234	C663R	4.02	4.64	3.4	high
235	R666Q	4.6	5.83	3.37	high
236	R666W	4.6	5.83	3.37	high
237	T672A	1.2	0.45	1.95	low
238	T672M	2.175	2.4	1.95	medium
239	G675S	2.43	2.15	2.71	medium
240	M677I	1.14	-1.09	3.37	low
241	M677V	1.24	-0.19	2.67	low
242	M677T	3.75	4.13	3.37	high
243	V678A	3.27	3.71	2.83	medium
244	D681N	4.255	5.11	3.4	high
245	K682T	2.54	1.99	3.09	medium
246	R683Q	4.59	5.81	3.37	high
247	R683W	4.59	5.81	3.37	high
248	F684C	4.095	5.05	3.14	high
249	F684L	2.94	3.44	2.44	medium
250	R686H	2.5	1.96	3.04	medium
251	R686C	3.74	4.44	3.04	high
252	R686P	3.19	3.34	3.04	medium
253	R690P	3.555	4.07	3.04	high
254	R690Q	1.395	0.44	2.35	low
255	R690W	3.005	2.97	3.04	medium
256	K692N	2.465	2.53	2.4	medium
257	P694S	2.06	0.69	3.43	medium
258	R695H	1.685	1.29	2.08	low
259	R695P	1.57	1.06	2.08	low
260	R695S	0.89	-0.3	2.08	low
261	H700Y	-0.245	0.47	-0.96	neutral
262	T702I	1.62	2.14	1.1	low
263	A704V	1.53	2.37	0.69	low
264	N705D	0.25	-0.6	1.1	neutral
265	N705I	1.965	2.83	1.1	medium
266	N705S	0.075	0.44	-0.29	neutral
267	N707T	2.9	4.01	1.79	medium
268	T709I	2.085	2.56	1.61	medium
269	V710M	1.665	2.64	0.69	low
270	D711N	3.11	4.61	1.61	medium
271	D711Y	3.11	4.61	1.61	medium
272	G713R	0	0	0	neutral

273	A717G	2.54	4.39	0.69	medium
274	R722P	2.61	3.43	1.79	medium
275	M724T	2.545	3.99	1.1	medium
276	A725P	3.215	4.64	1.79	medium

Table 3:

Protein Stability prediction using computational servers

Protein Stability Prediction								
Sr.no	mCSM		SDM		DUET		STRUM	
	$\Delta\Delta G$	Prediction	$\Delta\Delta G$	Prediction	$\Delta\Delta G$	Prediction	$\Delta\Delta G$	Prediction
1	-0.782	Destabilizing	-1.43	Destabilizing	-0.732	Destabilizing	0.96	Stabilizing
2	-1.331	Destabilizing	0.35	Stabilizing	-0.875	Destabilizing	2.17	Stabilizing
3	-0.87	Destabilizing	0.8	Stabilizing	-0.495	Destabilizing	1.62	Stabilizing
4	-0.895	Destabilizing	0.57	Stabilizing	-0.246	Destabilizing	3.15	Stabilizing
5	0.272	Stabilizing	-0.13	Destabilizing	0.501	Stabilizing	-0.3	Destabilizing
6	-0.093	Destabilizing	0.1	Stabilizing	-0.239	Destabilizing	-0.39	Destabilizing
7	-0.167	Destabilizing	-0.83	Destabilizing	-0.264	Destabilizing	-1.33	Destabilizing
8	0.012	Stabilizing	0.12	Stabilizing	0.216	Stabilizing	3.89	Stabilizing
9	-0.91	Destabilizing	-1.48	Destabilizing	-0.933	Destabilizing	1.32	Stabilizing
10	-0.438	Destabilizing	-0.34	Destabilizing	-0.104	Destabilizing	2.86	Stabilizing
11	-0.606	Destabilizing	-2.2	Destabilizing	-0.693	Destabilizing	1.71	Stabilizing
12	-0.362	Destabilizing	0.05	Stabilizing	-0.011	Destabilizing	0.52	Stabilizing
13	-0.084	Destabilizing	1.97	Stabilizing	0.712	Stabilizing	3.47	Stabilizing
14	-1.41	Destabilizing	-4.41	Destabilizing	-2.096	Destabilizing	1.7	Stabilizing
15	-1.2	Destabilizing	0.02	Stabilizing	-0.629	Destabilizing	2.48	Stabilizing
16	-0.335	Destabilizing	0.84	Stabilizing	0.075	Stabilizing	1.24	Stabilizing
17	-0.067	Destabilizing	-0.05	Destabilizing	0.059	Stabilizing	0.37	Stabilizing
18	0.592	Stabilizing	0.46	Stabilizing	0.756	Stabilizing	0.09	Stabilizing
19	-0.461	Destabilizing	0.03	Stabilizing	-0.315	Destabilizing	1.65	Stabilizing
20	-0.918	Destabilizing	0.45	Stabilizing	-0.419	Destabilizing	0.88	Stabilizing
21	-0.93	Destabilizing	-0.18	Destabilizing	-0.639	Destabilizing	1.17	Stabilizing
22	-1.59	Destabilizing	-1.49	Destabilizing	-1.815	Destabilizing	-1.02	Destabilizing
23	-0.285	Destabilizing	-0.73	Destabilizing	-0.208	Destabilizing	1.3	Stabilizing
24	-1.306	Destabilizing	-0.11	Destabilizing	-1.222	Destabilizing	1.24	Stabilizing
25	-2.117	Destabilizing	-0.96	Destabilizing	-2.096	Destabilizing	0.06	Stabilizing
26	-1.033	Destabilizing	-0.39	Destabilizing	-0.988	Destabilizing	1.02	Stabilizing
27	0.244	Stabilizing	0.82	Stabilizing	0.613	Stabilizing	1.36	Stabilizing
28	-0.362	Destabilizing	0.23	Stabilizing	-0.09	Destabilizing	0.98	Stabilizing
29	-0.727	Destabilizing	-1.23	Destabilizing	-0.767	Destabilizing	0.24	Stabilizing
30	-0.444	Destabilizing	1.29	Stabilizing	0.15	Stabilizing	0.98	Stabilizing
31	-0.757	Destabilizing	0.69	Stabilizing	-0.399	Destabilizing	0.67	Stabilizing
32	-1.466	Destabilizing	-1.98	Destabilizing	-1.858	Destabilizing	-0.01	Destabilizing
33	-1.788	Destabilizing	-1.76	Destabilizing	-2.092	Destabilizing	-1.13	Destabilizing
34	-1.719	Destabilizing	-0.63	Destabilizing	-1.799	Destabilizing	-0.41	Destabilizing
35	-0.813	Destabilizing	-0.19	Destabilizing	-0.594	Destabilizing	0.31	Stabilizing
36	-1.158	Destabilizing	0.16	Stabilizing	-0.933	Destabilizing	0.56	Stabilizing
37	-0.629	Destabilizing	0.62	Stabilizing	-0.37	Destabilizing	-0.33	Destabilizing
38	0.031	Stabilizing	-0.39	Destabilizing	0.265	Stabilizing	0.69	Stabilizing
39	-1.281	Destabilizing	-1.19	Destabilizing	-1.099	Destabilizing	1.2	Stabilizing
40	0.221	Stabilizing	-0.46	Destabilizing	0.331	Stabilizing	1.18	Stabilizing
41	-1.134	Destabilizing	-0.41	Destabilizing	-0.914	Destabilizing	2.25	Stabilizing
42	-1.206	Destabilizing	-0.15	Destabilizing	-0.975	Destabilizing	1.94	Stabilizing
43	-0.432	Destabilizing	0.61	Stabilizing	0.112	Stabilizing	1.53	Stabilizing
44	-1.133	Destabilizing	-0.72	Destabilizing	-1.033	Destabilizing	-0.49	Destabilizing
45	-1.928	Destabilizing	-1.39	Destabilizing	-2.109	Destabilizing	-0.97	Destabilizing
46	-1.616	Destabilizing	-0.89	Destabilizing	-1.57	Destabilizing	-1.36	Destabilizing
47	-0.686	Destabilizing	-1.46	Destabilizing	-0.677	Destabilizing	2.23	Stabilizing
48	-0.992	Destabilizing	-0.72	Destabilizing	-1.05	Destabilizing	0.62	Stabilizing
49	0.253	Stabilizing	-0.4	Destabilizing	0.295	Stabilizing	0.06	Stabilizing
51	-0.58	Destabilizing	-0.7	Destabilizing	-0.51	Destabilizing	1.12	Stabilizing
52	-0.986	Destabilizing	0.18	Stabilizing	-0.753	Destabilizing	0.21	Stabilizing
53	-0.145	Destabilizing	0.4	Stabilizing	0.156	Stabilizing	0.48	Stabilizing
54	-1.161	Destabilizing	-0.69	Destabilizing	-1.01	Destabilizing	-0.18	Destabilizing
55	-0.331	Destabilizing	-0.35	Destabilizing	-0.322	Destabilizing	2.16	Stabilizing
56	-1.089	Destabilizing	-1.39	Destabilizing	-1.376	Destabilizing	3.43	Stabilizing
57	-1.241	Destabilizing	-3.02	Destabilizing	-1.344	Destabilizing	1.82	Stabilizing
58	-0.739	Destabilizing	-1.97	Destabilizing	-0.738	Destabilizing	1.03	Stabilizing
59	-1.167	Destabilizing	-0.95	Destabilizing	-1.224	Destabilizing	2.06	Stabilizing
60	-0.498	Destabilizing	1.42	Stabilizing	0.222	Stabilizing	1.29	Stabilizing
60	-0.556	Destabilizing	-0.14	Destabilizing	-0.198	Destabilizing	3	Stabilizing
61	-0.056	Destabilizing	-1.4	Destabilizing	-0.171	Destabilizing	-1.41	Destabilizing
62	-0.243	Destabilizing	-0.53	Destabilizing	-0.242	Destabilizing	-1.75	Destabilizing
63	-0.676	Destabilizing	-0.16	Destabilizing	-0.612	Destabilizing	-0.49	Destabilizing
64	-0.239	Destabilizing	0.34	Stabilizing	0.161	Stabilizing	1.41	Stabilizing
65	0.465	Stabilizing	3.13	Stabilizing	1.363	Stabilizing	3.94	Stabilizing
66	-0.87	Destabilizing	-0.78	Destabilizing	-1.011	Destabilizing	3.59	Stabilizing
67	-0.035	Destabilizing	-0.67	Destabilizing	-0.006	Destabilizing	0.72	Stabilizing
68	-0.372	Destabilizing	-0.58	Destabilizing	-0.176	Destabilizing	3.03	Stabilizing
69	-0.577	Destabilizing	-0.86	Destabilizing	-0.496	Destabilizing	1.39	Stabilizing
70	-1.772	Destabilizing	-1.01	Destabilizing	-1.725	Destabilizing	1.82	Stabilizing
71	-0.883	Destabilizing	-0.23	Destabilizing	-0.524	Destabilizing	0.76	Stabilizing
72	-0.669	Destabilizing	-0.61	Destabilizing	-0.439	Destabilizing	2.64	Stabilizing
73	-0.443	Destabilizing	-0.73	Destabilizing	-0.388	Destabilizing	2.58	Stabilizing
74	-0.772	Destabilizing	-0.39	Destabilizing	-0.495	Destabilizing	2.19	Stabilizing
75	-0.675	Destabilizing	2.26	Stabilizing	0.211	Stabilizing	1.67	Stabilizing

76	-0.66	Destabilizing	-1.12	Destabilizing	-0.6	Destabilizing	1.6	Stabilizing
77	-0.146	Destabilizing	-0.17	Destabilizing	-0.11	Destabilizing	-0.7	Destabilizing
78	-1.025	Destabilizing	0.15	Stabilizing	-0.864	Destabilizing	-0.39	Destabilizing
79	-0.469	Destabilizing	-0.26	Destabilizing	-0.288	Destabilizing	0.05	Stabilizing
80	-0.599	Destabilizing	0.95	Stabilizing	0.036	Stabilizing	2.68	Stabilizing
81	-0.326	Destabilizing	-2.07	Destabilizing	-0.598	Destabilizing	2.28	Stabilizing
82	-0.06	Destabilizing	0.880	Stabilizing	0.495	Stabilizing	2.22	Stabilizing
83	-0.466	Destabilizing	-0.43	Destabilizing	-0.336	Destabilizing	2.76	Stabilizing
84	-1.287	Destabilizing	-1.93	Destabilizing	-1.314	Destabilizing	1.93	Stabilizing
85	-0.596	Destabilizing	-0.01	Destabilizing	-0.315	Destabilizing	0.67	Stabilizing
86	-0.962	Destabilizing	-0.820	Destabilizing	-0.584	Destabilizing	1.81	Stabilizing
87	-0.835	Destabilizing	-0.25	Destabilizing	-0.518	Destabilizing	1.7	Stabilizing
88	-0.298	Destabilizing	-1.57	Destabilizing	-0.587	Destabilizing	1.94	Stabilizing
89	-0.677	Destabilizing	-0.28	Destabilizing	-0.57	Destabilizing	-0.38	Destabilizing
90	-1.431	Destabilizing	0.770	Stabilizing	-0.898	Destabilizing	-1.38	Destabilizing
91	-0.693	Destabilizing	-1.27	Destabilizing	-0.759	Destabilizing	-0.19	Destabilizing
92	-1.337	Destabilizing	-1.1	Destabilizing	-1.139	Destabilizing	1.84	Stabilizing
93	-0.233	Destabilizing	0.28	Stabilizing	0.047	Stabilizing	-0.18	Destabilizing
94	0.416	Stabilizing	-1.53	Destabilizing	0.324	Stabilizing	-0.54	Destabilizing
95	-1.163	Destabilizing	-1.73	Destabilizing	-1.367	Destabilizing	-0.35	Destabilizing
96	0.074	Stabilizing	0.11	Stabilizing	0.421	Stabilizing	1.25	Stabilizing
97	-1.255	Destabilizing	-0.79	Destabilizing	-1.177	Destabilizing	-1.41	Destabilizing
98	-0.201	Destabilizing	-0.201	Destabilizing	-0.434	Destabilizing	-0.37	Destabilizing
99	-0.296	Destabilizing	-0.14	Destabilizing	-0.004	Destabilizing	2.14	Stabilizing
100	-0.155	Destabilizing	-0.1	Destabilizing	0.045	Stabilizing	-0.56	Destabilizing
101	0.116	Stabilizing	-0.75	Destabilizing	0.267	Stabilizing	0.93	Stabilizing
102	-1.023	Destabilizing	-1.53	Destabilizing	-1.087	Destabilizing	1.72	Stabilizing
103	0.043	Stabilizing	-0.58	Destabilizing	-0.035	Destabilizing	1.74	Stabilizing
104	-0.143	Destabilizing	-0.24	Destabilizing	0.07	Stabilizing	0.66	Stabilizing
105	0.125	Stabilizing	0.78	Stabilizing	0.409	Stabilizing	0.75	Stabilizing
106	-0.822	Destabilizing	1.030	Stabilizing	-0.194	Destabilizing	2.72	Stabilizing
107	0.007	Stabilizing	0.69	Stabilizing	0.607	Stabilizing	0.97	Stabilizing
108	-0.126	Destabilizing	-0.49	Destabilizing	0.205	Stabilizing	0.45	Stabilizing
109	-0.617	Destabilizing	-0.31	Destabilizing	-0.467	Destabilizing	2.02	Stabilizing
110	-1.082	Destabilizing	-0.39	Destabilizing	-1.089	Destabilizing	0.01	Stabilizing
111	0.075	Stabilizing	1.3	Stabilizing	0.576	Stabilizing	2.53	Stabilizing
112	-0.908	Destabilizing	-1.4	Destabilizing	-1.038	Destabilizing	0.58	Stabilizing
113	-0.264	Destabilizing	0.100	Stabilizing	-0.355	Destabilizing	-0.12	Destabilizing
114	-1.842	Destabilizing	-0.37	Destabilizing	-2.011	Destabilizing	-0.06	Destabilizing
115	-1.052	Destabilizing	0	Stabilizing	-0.927	Destabilizing	1.44	Stabilizing
116	-0.404	Destabilizing	3.38	Stabilizing	0.629	Stabilizing	2.62	Stabilizing
117	-2.477	Destabilizing	-0.71	Destabilizing	-2.31	Destabilizing	1.65	Stabilizing
118	-0.113	Destabilizing	1.28	Stabilizing	0.536	Stabilizing	3.15	Stabilizing
119	-1.829	Destabilizing	-1.17	Destabilizing	-1.856	Destabilizing	2.81	Stabilizing
120	-3.028	Destabilizing	-3.48	Destabilizing	-3.24	Destabilizing	0.55	Stabilizing
121	-0.873	Destabilizing	-2.63	Destabilizing	-1.173	Destabilizing	0.94	Stabilizing
122	-0.277	Destabilizing	0.36	Stabilizing	0.216	Stabilizing	2.47	Stabilizing
123	-0.746	Destabilizing	-0.8	Destabilizing	-0.694	Destabilizing	0.91	Stabilizing
124	-1.079	Destabilizing	0.81	Stabilizing	-0.623	Destabilizing	-0.53	Destabilizing
125	-0.697	Destabilizing	0.370	Stabilizing	-0.202	Destabilizing	-0.27	Destabilizing
126	-1.189	Destabilizing	-0.75	Destabilizing	-1.039	Destabilizing	1.16	Stabilizing
127	-1.101	Destabilizing	0.15	Stabilizing	-1.023	Destabilizing	0.59	Stabilizing
128	-0.412	Destabilizing	0.34	Stabilizing	-0.243	Destabilizing	1.68	Stabilizing
129	-0.268	Destabilizing	0.82	Stabilizing	0.248	Stabilizing	0.54	Stabilizing
130	-0.326	Destabilizing	0.05	Stabilizing	0.044	Stabilizing	0.56	Stabilizing
131	-0.661	Destabilizing	-0.52	Destabilizing	-0.405	Destabilizing	1.06	Stabilizing
132	-0.538	Destabilizing	-0.21	Destabilizing	-0.276	Destabilizing	2.76	Stabilizing
133	-0.47	Destabilizing	-0.32	Destabilizing	-0.043	Destabilizing	1.44	Stabilizing
134	-0.787	Destabilizing	0.04	Stabilizing	-0.617	Destabilizing	0.68	Stabilizing
135	-1.078	Destabilizing	-2.32	Destabilizing	-1.169	Destabilizing	1.98	Stabilizing
136	-0.114	Destabilizing	2.26	Stabilizing	0.74	Stabilizing	2.96	Stabilizing
137	-1.256	Destabilizing	-2.85	Destabilizing	-1.642	Destabilizing	1.27	Stabilizing
138	-0.125	Destabilizing	1.26	Stabilizing	0.408	Stabilizing	2.14	Stabilizing
139	-0.335	Destabilizing	-0.270	Destabilizing	-0.364	Destabilizing	-0.98	Destabilizing
140	-0.706	Destabilizing	0.26	Stabilizing	-0.638	Destabilizing	-0.4	Destabilizing
141	0.302	Stabilizing	-0.46	Destabilizing	0.213	Stabilizing	-1.47	Destabilizing
142	-0.405	Destabilizing	0.19	Stabilizing	-0.241	Destabilizing	2.88	Stabilizing
143	-0.815	Destabilizing	1.17	Stabilizing	-0.138	Destabilizing	2.98	Stabilizing
144	0.346	Stabilizing	0.28	Stabilizing	0.617	Stabilizing	1.71	Stabilizing
145	-1.334	Destabilizing	-2.38	Destabilizing	-1.62	Destabilizing	1.42	Stabilizing
146	-1.196	Destabilizing	-2.82	Destabilizing	-1.752	Destabilizing	-0.46	Destabilizing
147	-0.091	Destabilizing	-0.52	Destabilizing	-0.075	Destabilizing	2.58	Stabilizing
148	-0.269	Destabilizing	-0.5	Destabilizing	-0.25	Destabilizing	-0.28	Destabilizing
149	-0.551	Destabilizing	-0.48	Destabilizing	-0.442	Destabilizing	0.61	Stabilizing
150	-1.854	Destabilizing	-2.9	Destabilizing	-2.096	Destabilizing	-0.24	Destabilizing
151	-0.827	Destabilizing	2.630	Stabilizing	0.138	Stabilizing	2.35	Stabilizing
152	-0.054	Destabilizing	-0.57	Destabilizing	-0.008	Destabilizing	-0.38	Destabilizing
153	-2.282	Destabilizing	-1.57	Destabilizing	-2.327	Destabilizing	1.11	Stabilizing
154	-0.496	Destabilizing	-0.28	Destabilizing	-0.151	Destabilizing	1.68	Stabilizing
155	-0.424	Destabilizing	-1.24	Destabilizing	-0.319	Destabilizing	1.1	Stabilizing
156	-0.725	Destabilizing	0.25	Stabilizing	-0.482	Destabilizing	2.54	Stabilizing
157	-0.711	Destabilizing	0.31	Stabilizing	-0.2	Destabilizing	1.55	Stabilizing
158	-0.58	Destabilizing	-0.61	Destabilizing	-0.206	Destabilizing	0.7	Stabilizing
159	-0.484	Destabilizing	0.33	Stabilizing	-0.079	Destabilizing	-1.15	Destabilizing
160	-0.904	Destabilizing	-3.12	Destabilizing	-1.094	Destabilizing	2.93	Stabilizing
161	0.195	Stabilizing	0.1	Stabilizing	-0.043	Destabilizing	-0.1	Destabilizing
162	-1.619	Destabilizing	-0.92	Destabilizing	-1.648	Destabilizing	1.68	Stabilizing
163	-2.073	Destabilizing	-1.82	Destabilizing	-2.074	Destabilizing	1.95	Stabilizing
164	-1.074	Destabilizing	0.78	Stabilizing	-0.363	Destabilizing	3.12	Stabilizing
165	-1.092	Destabilizing	-0.86	Destabilizing	-1.149	Destabilizing	3.59	Stabilizing
166	-0.247	Destabilizing	-0.24	Destabilizing	-0.222	Destabilizing	-1.75	Destabilizing
167	-0.244	Destabilizing	-1.000	Destabilizing	-0.288	Destabilizing	-1.89	Destabilizing

168	0.277	Stabilizing	0.2	Stabilizing	0.418	Stabilizing	-1.05	Destabilizing
169	0.05	Stabilizing	-0.81	Destabilizing	-0.066	Destabilizing	-0.26	Destabilizing
170	-0.642	Destabilizing	-0.79	Destabilizing	-0.525	Destabilizing	1.09	Stabilizing
171	-0.805	Destabilizing	-0.97	Destabilizing	-0.65	Destabilizing	1.36	Stabilizing
172	-0.882	Destabilizing	-2.54	Destabilizing	-1.2	Destabilizing	1.89	Stabilizing
173	-0.69	Destabilizing	0.05	Stabilizing	-0.646	Destabilizing	1.51	Stabilizing
174	-0.332	Destabilizing	0.32	Stabilizing	-0.102	Destabilizing	1.59	Stabilizing
175	-0.335	Destabilizing	0.31	Stabilizing	-0.401	Destabilizing	-0.62	Destabilizing
176	0.105	Stabilizing	-0.11	Destabilizing	0.399	Stabilizing	0.31	Stabilizing
177	-0.762	Destabilizing	-0.88	Destabilizing	-0.534	Destabilizing	1.62	Stabilizing
178	-0.669	Destabilizing	-0.43	Destabilizing	-0.554	Destabilizing	2.64	Stabilizing
179	-0.521	Destabilizing	0.28	Stabilizing	-0.575	Destabilizing	-0.48	Destabilizing
180	-1.544	Destabilizing	-1.39	Destabilizing	-1.807	Destabilizing	2.19	Stabilizing
181	0.012	Stabilizing	0.47	Stabilizing	0.277	Stabilizing	2.79	Stabilizing
182	-0.427	Destabilizing	-0.44	Destabilizing	-0.285	Destabilizing	2.48	Stabilizing
183	-1.735	Destabilizing	-2.1	Destabilizing	-1.899	Destabilizing	2.16	Stabilizing
184	-0.605	Destabilizing	-2.39	Destabilizing	-0.984	Destabilizing	1.35	Stabilizing
185	-2.751	Destabilizing	-3.72	Destabilizing	-3.067	Destabilizing	0.1	Stabilizing
186	-0.583	Destabilizing	-0.15	Destabilizing	-0.341	Destabilizing	0.92	Stabilizing
187	-0.029	Destabilizing	-1.61	Destabilizing	-0.163	Destabilizing	0.86	Stabilizing
188	-0.762	Destabilizing	0.18	Stabilizing	-0.199	Destabilizing	2.33	Stabilizing
189	0.007	Stabilizing	-0.46	Destabilizing	0.325	Stabilizing	1.49	Stabilizing
190	-0.21	Destabilizing	-0.69	Destabilizing	0.011	Stabilizing	1.81	Stabilizing
191	-1.033	Destabilizing	0.62	Stabilizing	-0.584	Destabilizing	1.54	Stabilizing
192	-0.545	Destabilizing	-0.8	Destabilizing	-0.423	Destabilizing	2.46	Stabilizing
193	-0.014	Destabilizing	0.140	Stabilizing	0.361	Stabilizing	0.69	Stabilizing
194	-0.956	Destabilizing	-0.45	Destabilizing	-0.972	Destabilizing	2.24	Stabilizing
195	-0.136	Destabilizing	2.51	Stabilizing	0.534	Stabilizing	-0.63	Destabilizing
196	-0.46	Destabilizing	0.19	Stabilizing	-0.016	Destabilizing	2.16	Stabilizing
197	-1.733	Destabilizing	-3.12	Destabilizing	-2.005	Destabilizing	1.6	Stabilizing
198	-1.085	Destabilizing	-2.87	Destabilizing	-1.46	Destabilizing	-1.43	Destabilizing
199	-0.006	Destabilizing	-1.591	Destabilizing	-0.111	Stabilizing	1.42	Stabilizing
200	-0.78	Destabilizing	-0.01	Destabilizing	-0.539	Destabilizing	1.78	Stabilizing
201	-0.1	Destabilizing	-0.17	Destabilizing	0.210	Stabilizing	0.98	Stabilizing
202	-2.028	Destabilizing	-1.09	Destabilizing	-2.16	Destabilizing	-1.52	Destabilizing
203	-2.193	Destabilizing	-0.65	Destabilizing	-2.271	Destabilizing	-0.78	Destabilizing
204	-1.729	Destabilizing	-1.85	Destabilizing	-2.095	Destabilizing	-2.07	Destabilizing
205	-1.016	Destabilizing	-1.05	Destabilizing	-0.879	Destabilizing	2.69	Stabilizing
206	-1.769	Destabilizing	-0.83	Destabilizing	-1.981	Destabilizing	2.32	Stabilizing
207	-0.62	Destabilizing	-0.35	Destabilizing	-0.296	Destabilizing	1.48	Stabilizing
208	-0.471	Destabilizing	-1.08	Destabilizing	-0.404	Destabilizing	1.76	Stabilizing
209	-0.877	Destabilizing	-0.76	Destabilizing	-0.932	Destabilizing	1.74	Stabilizing
210	-0.486	Destabilizing	0.22	Stabilizing	-0.106	Destabilizing	1.56	Stabilizing
211	-1.274	Destabilizing	-0.2	Destabilizing	-1.204	Destabilizing	1.09	Stabilizing
212	-0.579	Destabilizing	-1	Destabilizing	-0.77	Destabilizing	-0.56	Destabilizing
213	-0.903	Destabilizing	-0.72	Destabilizing	-0.89	Destabilizing	0.67	Stabilizing
214	-0.131	Destabilizing	0.08	Stabilizing	-0.312	Destabilizing	1.26	Stabilizing
215	-0.297	Destabilizing	-0.6	Destabilizing	-0.017	Destabilizing	3.01	Stabilizing
216	-1.334	Destabilizing	-2.38	Destabilizing	-1.62	Destabilizing	1.41	Stabilizing
217	0.904	Stabilizing	-1.88	Destabilizing	-1.62	Destabilizing	1.83	Stabilizing
218	-0.575	Destabilizing	-0.42	Destabilizing	-0.365	Destabilizing	2.65	Stabilizing
219	-0.297	Destabilizing	0.13	Stabilizing	0.055	Stabilizing	1.97	Stabilizing
220	-0.101	Destabilizing	0.86	Stabilizing	0.34	Stabilizing	1.97	Stabilizing
221	-0.521	Destabilizing	0.6	Stabilizing	-0.37	Destabilizing	0.76	Stabilizing
222	-1.464	Destabilizing	0.57	Stabilizing	-1.285	Destabilizing	-0.12	Destabilizing
223	0.157	Stabilizing	0.58	Stabilizing	0.324	Stabilizing	-0.86	Destabilizing
224	-0.135	Destabilizing	-1.21	Destabilizing	-0.476	Destabilizing	-1.47	Destabilizing
225	-0.907	Destabilizing	-0.56	Destabilizing	-0.75	Destabilizing	2.18	Stabilizing
226	-0.086	Destabilizing	0.57	Stabilizing	0.428	Stabilizing	0.39	Stabilizing
227	-0.522	Destabilizing	-0.97	Destabilizing	-0.372	Destabilizing	2.35	Stabilizing
228	-0.256	Destabilizing	2.43	Stabilizing	0.603	Stabilizing	0.73	Stabilizing
229	-1.447	Destabilizing	-1.53	Destabilizing	-1.551	Destabilizing	2.71	Stabilizing
230	-1.5	Destabilizing	-0.74	Destabilizing	-1.625	Destabilizing	0.43	Stabilizing
231	-1.405	Destabilizing	-1.76	Destabilizing	-1.721	Destabilizing	-1	Destabilizing
232	0.839	Stabilizing	0.25	Stabilizing	1.072	Stabilizing	0.92	Stabilizing
233	-1.967	Destabilizing	-3.05	Destabilizing	-2.237	Destabilizing	-0.21	Destabilizing
234	-1.058	Destabilizing	-1.76	Destabilizing	-0.933	Destabilizing	0.47	Stabilizing
235	-1.384	Destabilizing	-0.63	Destabilizing	-1.257	Destabilizing	-1.45	Destabilizing
236	-1.445	Destabilizing	0.72	Stabilizing	-0.979	Destabilizing	-0.75	Destabilizing
237	-0.231	Destabilizing	0.32	Stabilizing	0.004	Stabilizing	0.8	Stabilizing
238	-0.048	Destabilizing	0.01	Stabilizing	-0.042	Destabilizing	1.45	Stabilizing
239	-1.747	Destabilizing	-2.35	Destabilizing	-1.849	Destabilizing	3.59	Stabilizing
240	-1.437	Destabilizing	0.62	Stabilizing	-0.787	Destabilizing	3.42	Stabilizing
241	-1.845	Destabilizing	0.4	Stabilizing	-1.282	Destabilizing	2.49	Stabilizing
242	-2.251	Destabilizing	-2.02	Destabilizing	-2.142	Destabilizing	1.82	Stabilizing
243	-2.015	Destabilizing	-2.66	Destabilizing	-2.436	Destabilizing	0.08	Stabilizing
244	-0.525	Destabilizing	-0.08	Destabilizing	-0.319	Destabilizing	1.92	Stabilizing
245	-0.347	Destabilizing	-0.18	Destabilizing	-0.222	Destabilizing	-0.23	Destabilizing
246	-0.434	Destabilizing	-0.55	Destabilizing	-0.445	Destabilizing	0.27	Stabilizing
247	-0.255	Destabilizing	0.14	Stabilizing	-0.435	Destabilizing	0.05	Stabilizing
248	-1.735	Destabilizing	-1.12	Destabilizing	-1.75	Destabilizing	2.53	Stabilizing
249	-1.265	Destabilizing	-1.53	Destabilizing	-1.358	Destabilizing	3.23	Stabilizing
250	-0.781	Destabilizing	-0.39	Destabilizing	-0.795	Destabilizing	-0.26	Destabilizing
251	0.104	Stabilizing	-0.61	Destabilizing	0.051	Stabilizing	-1.75	Destabilizing
252	0.468	Stabilizing	-1.65	Destabilizing	0.091	Stabilizing	-2.3	Destabilizing
253	0.058	Stabilizing	-1.65	Destabilizing	-0.277	Destabilizing	-1.26	Destabilizing
254	-0.196	Destabilizing	-0.87	Destabilizing	-0.145	Destabilizing	-0.2	Destabilizing
255	-0.183	Destabilizing	0.04	Stabilizing	-0.311	Destabilizing	-0.67	Destabilizing
256	-0.883	Destabilizing	-0.66	Destabilizing	-0.81	Destabilizing	1.17	Stabilizing
257	-0.679	Destabilizing	-0.34	Destabilizing	-0.530	Destabilizing	1.74	Stabilizing
258	-1.459	Destabilizing	0.35	Stabilizing	-1.337	Destabilizing	0.2	Stabilizing
259	-0.034	Destabilizing	-1	Destabilizing	-0.263	Destabilizing	-0.99	Destabilizing
260	-0.782	Destabilizing	-1.18	Destabilizing	-0.95	Destabilizing	-0.92	Destabilizing
261	0.859	Stabilizing	-0.06	Destabilizing	1.013	Stabilizing	0.87	Stabilizing

262	-0.166	Destabilizing	1.93	Stabilizing	0.584	Stabilizing	2.23	Stabilizing
263	-0.285	Destabilizing	0.39	Stabilizing	0.125	Stabilizing	1.88	Stabilizing
264	-0.607	Destabilizing	-0.01	Destabilizing	-0.288	Destabilizing	1.93	Stabilizing
265	-0.037	Destabilizing	0.48	Stabilizing	0.304	Stabilizing	2.76	Stabilizing
266	-0.411	Destabilizing	-0.94	Destabilizing	-0.322	Destabilizing	1.28	Stabilizing
267	-0.513	Destabilizing	-0.57	Destabilizing	-0.334	Destabilizing	0.34	Stabilizing
268	-0.059	Destabilizing	0.49	Stabilizing	0.293	Stabilizing	1.58	Stabilizing
269	-0.661	Destabilizing	-0.35	Destabilizing	-0.59	Destabilizing	2.23	Stabilizing
270	-0.083	Destabilizing	-0.16	Destabilizing	0.064	Stabilizing	0.4	Stabilizing
271	-0.119	Destabilizing	0.360	Stabilizing	-0.073	Destabilizing	0.47	Stabilizing
272	-1.214	Destabilizing	1.62	Stabilizing	-0.628	Destabilizing	2.38	Stabilizing
273	-0.885	Destabilizing	-1.58	Destabilizing	-0.927	Destabilizing	1.79	Stabilizing
274	0.183	Stabilizing	-1.65	Destabilizing	-0.168	Destabilizing	-1.87	Destabilizing
275	-0.106	Destabilizing	-1.28	Destabilizing	0.202	Stabilizing	1.14	Stabilizing
276	-0.304	Destabilizing	-1.46	Destabilizing	-0.261	Destabilizing	1.72	Stabilizing

Table 4:
Prediction Cancer association using FATHMM Server

Cancer Association		
Sr.no	Mutation	Prediction
1	R30C	PASSENGER/OTHER
2	G47R	CANCER
3	K48R	CANCER
4	T49I	PASSENGER/OTHER
5	R75I	CANCER
6	R112C	PASSENGER/OTHER
7	R112G	PASSENGER/OTHER
8	R112H	PASSENGER/OTHER
9	R186C	PASSENGER/OTHER
10	Y209C	PASSENGER/OTHER
11	R227C	PASSENGER/OTHER
12	V231M	PASSENGER/OTHER
13	R253C	PASSENGER/OTHER
14	R287Y	PASSENGER/OTHER
15	R324H	CANCER
16	F403C	PASSENGER/OTHER
17	F403S	PASSENGER/OTHER
18	L406P	PASSENGER/OTHER
19	E419G	PASSENGER/OTHER
20	E419K	PASSENGER/OTHER
21	S441T	PASSENGER/OTHER
22	S462P	PASSENGER/OTHER
23	P468L	PASSENGER/OTHER
24	M483T	PASSENGER/OTHER
25	L485P	PASSENGER/OTHER
26	V488A	PASSENGER/OTHER
27	I494F	PASSENGER/OTHER
28	R497C	PASSENGER/OTHER
29	R511W	PASSENGER/OTHER
30	R518W	PASSENGER/OTHER
31	G534D	PASSENGER/OTHER
32	V536M	PASSENGER/OTHER
33	F538S	PASSENGER/OTHER
34	Y542C	PASSENGER/OTHER
35	R592C	PASSENGER/OTHER
36	R592H	PASSENGER/OTHER
37	R592P	PASSENGER/OTHER
38	G593R	PASSENGER/OTHER
39	G607A	PASSENGER/OTHER
40	R616P	PASSENGER/OTHER
41	R616Q	PASSENGER/OTHER
42	R616W	PASSENGER/OTHER
43	G622V	PASSENGER/OTHER
44	I632C	PASSENGER/OTHER
45	A635V	PASSENGER/OTHER
46	R658H	PASSENGER/OTHER
47	R658G	PASSENGER/OTHER
48	C663R	PASSENGER/OTHER
49	R666Q	PASSENGER/OTHER
51	R666W	PASSENGER/OTHER
52	G675S	PASSENGER/OTHER
53	M677T	PASSENGER/OTHER
54	V678A	PASSENGER/OTHER
55	D681N	CANCER
56	R683Q	CANCER
57	R683W	CANCER
58	F684C	PASSENGER/OTHER
59	R686C	PASSENGER/OTHER
60	R686P	PASSENGER/OTHER
60	R690P	PASSENGER/OTHER
61	R690W	PASSENGER/OTHER
62	D711N	PASSENGER/OTHER
63	M724T	PASSENGER/OTHER
64	A725P	PASSENGER/OTHER

Supplementary Table 1:

C-score predicted using I-TASSER Server

Sr.No	Predicted Models (I-TASSER)	C-score
1	Model 1	-1.59
2	Model 2	-2.98
3	Model 3	-3.63
4	Model 4	-3.44
5	Model 5	-2.42