In Silico Structural Modeling of Wildtype and Mutant PRODH Proteins Involved in Psychiatric Disorder.

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Research Article

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Abstract

Proline dehydrogenase is an important mitochondrial enzyme that is encoded by the *PRODH* gene. Biologically, a mutation in this gene affects the activity of proline dehydrogenase enzyme that is normally involved in conversion of proline to glutamate. However, its reduced or null activity leads to excess quantity of proline in the body, which results in different psychiatric phenotypes along with intellectual disability. In the present study, we performed *in silico* analysis on all reported mutations of *PRODH*. The 3D models of normal and mutant PRODH were predicted using I-TASSER. The predicted structures were visualized and superimposed using chimera 1.13.1. The CASTp was used to identify active sites in modelled proteins. Protein-protein docking was done with Cluspro, while protein-substrate docking was done with Auto Dock 1.5.6 and-MGL tools and the results were visualized using LigPlus+ v.2.2 and Discovery studio 2020 respectively. Alignment of 3D models (mutant with wildtype) revealed that Arg185Gln (73.83 %) and Gln19Ter (6.25%) had the highest and lowest similarity indices, respectively. Enzyme pocket prediction identified three largest sites, with the second largest active site pocket containing substrate proline binding residues Leu527, Tyr548, and Arg563. Moreover, docking of mutant and wildtype PRODH with its close interactor "ALDH4A1" showed differences with respect to number, position, and nature of interacting amino acids residues. We observed that the nature of amino acid substitution and the number of bonds affect the binding of proline molecule with proline dehydrogenase enzyme, and therefore, affect its biological activity.

Introduction

Proline dehydrogenase, also known as proline oxidase, is a mitochondrial enzyme, encoded by *PRODH* gene. Proline dehydrogenase enzyme mostly found in the brain, kidney and liver. Within the cells, proline dehydrogenase has role in energy production (Campbell et al. 1997; Goodman et al. 2000). Biochemically, this enzyme is involved in catabolism of amino acid proline by first converting it to pyrroline-5-carboxylate. The following step converts this intermediary product to the amino acid known as glutamate (Hoogendoorn et al. 2004). The conversion between these two amino acid i.e. proline and glutamate, within the cell is very vital in keeping a supply of the amino acids required for protein production and also for the transfer of energy (Jacquet et al. 2003,2005). Decreased function of proline dehydrogenase enzyme results in the accumulation of amino acid proline in the body (hyperprolinemia) (Campbell et al. 1997) with reduced level of glutamate. And, in severe cases of hyperprolinemia, it may cause intellectual disability (ID), kidney failure, seizures, psychiatric problems and/ or other neurological phenotypes (Campbell et al. 1997). Researchers believe that accumulation of proline may affect the action of different chemicals in the body that acts as neurotransmitters, and result in different psychiatric disorders such as schizophrenia (Li and He 2006; Li et al. 2004).

HGMD database has enlisted 24 missense/nonsense mutations in the *PRODH* gene to be involved in affecting the activity of proline dehydrogenase enzyme. Among these 24 reported mutations, 22 mutations substitute one amino acid with another amino acid (missense mutation) (Bender et al. 2005; Guilmatre et al. 2010; Jang et al. 2013), while only 2 mutations results in early truncation of the PRODH protein (non-sense mutations) (Raux et al. 2007; Kozakov et al. 2013). Most of these reported mutations compromise the efficacy of proline dehydrogenase enzyme (Jacquet et al. 2002, 2003).

The current *in silico* study was designed to check and compare the functional impact of all reported mutations in PRODH enzyme through protein modeling and docking, taking into account the aforementioned evidence.

Methodology

The data of all reported mutations in *PRODH* were obtained from HGMD database (Stenso et al. 2020), while the protein sequence was obtained from Ensemble genome browser (Ensembl genome browser 103. Ensembl.org. Accessed March 15, 2021. https://asia.ensembl.org/index.htm).

For structural analysis of normal and all PRODH mutants, 3D models were predicted using I-TASSER (Yang et al. 2015). Models with highest C-score were selected for further investigations. Visualization of 3D models were done using UCSF Chimera 1.13.1 (Pettersen et al. 2004). To investigate the differences caused by mutations, 3D models of normal and all mutant PRODH were superimposed using the Chimera.

Protein-protein docking, for normal and all mutant PRODH with their close functional interactor ALDH4A1, was done using online tool Cluspro (Kozakov et al. 2017). However, the close functional interactor of PRODH was predicted through String v9.1 database (Franceschini et al. 2013). Similarly, protein-substrate docking of normal and mutant PRODH with proline molecule was carried out through Autodock Vina and-MGL (Gaillard, 2018). The protein-substrate docked complexed were analyze through discovery studio 2020. Nonetheless, enzyme active site or binding pockets of wildtype PRODH were predicted using online tool CASTp (Binkowski et al. 2003).

Results

In general, it was observed that amino acid polarity and structure of side chain had significant impact on enzyme activity. For example, Pro406Leu and Leu441Pro, where cyclic amino acids were being replaced by aliphatic amino acids, showed severe effect. While, mild to moderate effect was observed where nonpolar but neutral amino acids were replaced by polar but uncharged amino acids and vice versa. However, this classification is very weak and cannot be implemented on all cases. The structural findings are described as follows;

Structural Analysis

The 3D models of all reported PRODH mutations (Supplementary Fig. 1) were superimposed with 3D models of wild-type PRODH protein (Fig. 1). The manual comparison of these models observed remarkable structural differences, which were measured in the form of similarity indices.

Among all the models, highest similarity index of wild-type PRODH protein with mutant was shown by Arg185Gln (73.83%), while the lowest similarity index was shown by mutant Leu441Pro + Leu441Pro/ Arg453Cys and Thr466Met + Thr466Met/Arg453Cys, which was 41.17% (Fig. 2).Complete detail of similarity

indices of all the models are summarized in Table 1.

Table 1
Nature of wild-type and Substituted amino acids in mutant PRODH protein.

Mutation	Nature of Mutation						Effect on enzyme activity	Similarity Index of mutant and normal protein	References
	Wild-type amino acid			Substituted Amino Acid					
	Class	Polarity	Charge	Class	Polarity	Charge			
Pro8Leu	Cyclic	Nonpolar	Neutral	Aliphatic	Nonpolar	Neutral	Moderate	69.33%	Jang et al. 2013
Arg11Pro	Basic	Basic polar	Positive	Cyclic	Nonpolar	Neutral	Mild	72.83%	Guilmatre et al. 2010
Gln19Pro	Amide	Polar	Neutral	Cyclic	Nonpolar	Neutral	Moderate	66.11%	Bender et al. 2005
Gln19Term	Amide	Polar	Neutral	Termination occurred			Severe	6.25%	Raux et al. 2007
Pro30Ser	Cyclic	Nonpolar	Neutral	Hydroxylic	Polar	Neutral	Mild	58.50%	Guilmatre et al. 2010
Ala58Thr	Aliphatic	Nonpolar	Neutral	Hydroxylic	Polar	Neutral	Moderate	68.33%	Guilmatre et al. 2010
Ala167Val	Aliphatic	Nonpolar	Neutral	Aliphatic	Nonpolar	Neutral	Moderate	69.17%	Bender et al. 2005
Arg185Gln	Basic	Basic polar	Positive	Amide	Polar	Neutral	Mild	73.83%	Bender et al. 2005
Arg185Trp	Basic	Basic polar	Positive	Aromatic	Nonpolar	Neutral	Moderate	61.33%	Bender et al. 2005
Thr275Asn	Hydroxylic	Polar	Neutral	Amide	Polar	Neutral	No detrimental effect	58.00%	Guilmatre et al. 2010
Leu289Met	Aliphatic	Nonpolar	Neutral	Sulfuric	Nonpolar	Neutral	Mild	43.17%	Bender et al. 2005
Pro406Leu	Cyclic	Nonpolar	Neutral	Aliphatic	Nonpolar	Neutral	Severe	56.83%	Bender et al. 2005
Asp426Asn	Acid	Acidic polar	Negative	Amide	Polar	Neutral	Moderate	52.00%	Bender et al. 2005
Val427Met	Aliphatic	Nonpolar	Neutral	Sulfuric	Nonpolar	Neutral	Moderate	57.67%	Bender et al. 2005
Arg431His	Basic	polar	Positive	Aromatic	Basic polar	Positive,	Moderate	66.33%	Bender et al. 2005
Leu441Pro	Aliphatic	Nonpolar	Neutral	Cyclic	Nonpolar	Neutral	Severe	65.00%	Bender et al. 2005
Gly444Asp	Aliphatic	Nonpolar	Neutral	Acid	Acidic polar	Negative	Severe	61.50%	Jang et al. 2013
Arg453Cys	Basic	Basic polar	Positive	Sulfuric	Nonpolar	Neutral	Severe	68.00%	Bender et al. 2005
Ala455Ser	Aliphatic	Nonpolar	Neutral	Hydroxylic	Polar	Neutral	Mild	57.83%	Bender et al. 2005
Thr466Met	Hydroxylic	Polar	Neutral	Sulfuric	Nonpolar	Neutral	Severe	51.50%	Bender et al. 2005
Ala472Thr	Aliphatic	Nonpolar	Neutral	Hydroxylic	Polar	Neutral	Mild	57.67%	Bender et al. 2005
Gln521Glu	Amide	Polar	Neutral	Acid	Acidic polar	Negative	Severe	61.00	Bender et al. 2005
Gln521Arg	Amide	Polar	Neutral	Basic	Basic polar	Positive	Enhance activity	58.67%	Bender et al. 2005
Gln526Term	Amide	Polar	Neutral	Termination occurred			Unknown effect	61.60%	Hu et al. 2014

Table 2
Number of bonds and nature of amino acids docked with substrate proline molecule in all reported PRODH protein mutations

Mutation	Number and nature of bonding				Position and nature of bonded amino acid			
	H bond	Alkyl bond	C-H bond	Unfavorable bonds	Polar	Non-Polar	Basic polar	Acidic Polar
Wild-type	2	1			Tyr548	Leu527	Arg563	
Pro8Leu	5	4	1			Ala496,Val442,Leu527,Gly444	His498,Arg443	Glu567
Arg11Pro	4	1				Gly229,Phe301,Trp300	Arg224	Asp228
Gln19Pro	2	1				Leu150		Glu147,Glu556
Gln19Term	Unable to dock with proline molecule due to small truncated protein							
Pro30Ser	4	2			Gln123,Tyr144	Gly552,Phe187	Arg217	Glu121
Ala58Thr	1	1			Thr411	Ala381		
Ala167Val	3	4				Leu527,Val442,Ala496	Arg564,His498	Glu567,Asp178
Arg185Gln	2	2			Asn410	Ala491,Val427		Asp426
Arg185Trp	2	2		1	Ser569	Val46,Pro49	Arg324	
Thr275Asn	3	1		3	Gln123,Ser210, Tyr144,Thr214		Arg217	
Leu289Met	2	2	1		Gln533	Ala186,Ile534	Arg579	Glu500
Pro406Leu	1	1				Leu561		Glu60
Asp426Asn	1	3	1		Asn568	Ala52,Ala565,Phe113	Arg63	
Val427Met	2	3			Tyr560,Tyr548	Leu527	Arg563	Asp380
Arg431His	2	1	2		Asn499,Asn594	Leu595,Pro599,Gly574		
Leu441Pro	2		2		Thr112	Leu20,Phe17,Phe113		
Gly444Asp	2	1	2	1	Tyr467		Arg563	Asp444,Glu567
Arg453Cys	5	1			Tyr551,Gln123	Pro553	Arg217	Glu121
Ala455Ser	1	3	1		Tyr200	Met555,Phe201,Trp254		Glu148
Thr466Met	2	2		2	Asn499	Val442	His498,Arg443	Glu567
Ala472Thr	4	3			Tyr446, Tyr548	Leu527, Ala445	Arg563,Lys234	Asp380
Gln521Glu	1	3			Tyr144	Ala237,Leu238,Ile233		
Gln521Arg	3	1	2			Met555,Pro559	Lys207	Glu147,Glu154, Glu158
Gln526Term	2						Arg217	Asp122
Thr466Met + Thr466Met/Arg453Cys				1	580Gln			
Leu441Pro + Leu441Pro/Arg453Cys	No protein substrate bonding were noted just Van der waal forces were noted							

Active site predication.

The wild-type PRODH protein's active site prediction revealed three major active sites. Among the three largest active sites, the second largest pocket was found to contain amino acids involved in substrate binding (proline). Leu527, Tyr548 and Arg563 are among the substrate interacting amino acids. The complete description of amino acids and its position, present in these three largest pockets, are summarized in supplementary table 1. The top three largest active site pockets of PRODH protein are illustrated in Fig. 3. It was also observed that residues in which substitution resulted in severe effect on activity of proline dehydrogenase enzyme were mostly present in the 2nd largest active site pocket. These residues include Leu441, Gly444, Arg453, Thr466 and Gln521.While, residue Pro406, exhibiting severe effect on enzyme activity, was present in the 1st largest active pocket of PRODH protein.

Protein-Protein Docking.

Protein-protein docking was carried out between wild-type and all the mutant PRODH protein with their close interactor ALDH4A1 protein and remarkable differences in the interacting sites of wild-type and mutant PRODH proteins were observed. Docking revealed that wild-type PRODH protein interacts with

ALDH4A1 protein through 12 different residues i.e.Arg598, Arg451, Ala252, Arg225, Lys234, Ser26, Gln29, Trp254, Leu20, Ser248, Thr22 and Gln246 via 16 interactive forces (15 hydrogen bond and 1 unfavorable bond). However, among all the mutant PRODH proteins, Arg431His interacted with ALDH4A1 protein by 24 bonds (23 hydrogen and 1 unfavorable bond) via 19 different residues. While lowest interaction was shown by Thr466Met + Thr466Met/Arg453Cys protein, wherein the mutant protein interacted with ALDH4A1 through 5 bonds (4 hydrogen and 1 unfavorable bond) involving 4 different residues. Diagrammatic representations of all the protein-protein interaction between normal and mutant PRODH protein with close interactor are shown in Supplementary Fig. 3 (a,b,c).

Protein-Substrate docking.

To better understand the interaction mechanism of proline, a substrate, with the wild type as well as mutant proteins, protein-substrate dockings were also performed. Wild-type PRODH was interacting with proline molecule by 3 bonds (1 hydrogen and 2 alky bond) via three residues i.e. Arg563, Tyr548 and Leu527. Highest protein-substrate interaction was shown by Pro8Leu variant, wherein the mutant protein showed interaction with proline molecule by 10 bonds (5 hydrogen, 4 alky and 1 unfavorable bond) through 7 different residues. However, the lowest protein-substrate interaction was shown by Gln19Ter variant. Wherein the mutant Gln19Ter protein was unable to interact with the proline molecule due to short shortened structure. All the interacting residues of mutant PRODH proteins with proline molecule were different as compared to wild-type. 2D representations of all the protein-substrate interaction between wild-type and mutant PRODH protein with proline molecule are in shown in Fig. 4 & supplementary Fig. 2. Similarly, compound mutant i.e. Thr466Met + Thr466Met/Arg453Cys protein was interacting with proline molecule by only 1 bond (unfavorable Donor Donor Bond) through a single residue, and compound mutant Leu441Pro + Leu441Pro/Arg453Cys protein was unable to dock with proline molecule as shown in Fig. 2.

Discussion

PRODH gene is present on chromosome 22q11.21, a region that is also reported to be associated with the contiguous gene syndrome, DiGeorge syndrome. This gene consists of 15 exons and spans over 23.77 Kb of DNA. The translational product of largest transcript encodes 600 amino acids long protein (Jacquet et al. 2003). This protein acts as a proline dehydrogenase enzyme (also known as proline oxidase). Proline dehydrogenase is a mitochondrial enzyme that converts proline to Δ^1-pyrroline-5-carboxylate and then to glutamate. Glutamate is the chief excitatory neuro-transmitter in the brain (Jacquet et al. 2005). PRODH mainly express in brain, lungs liver and kidney. Any pathogenic DNA change (either homozygous or compound heterozygous) in *PRODH* result in a condition known as hyperprolinemia type 1(MIM#239500) and susceptibility to schizophrenia 4 (MIM# 600850). Mutation in *PRODH* basically affects the activity of proline dehydrogenase enzyme, which results in accumulation of proline and deficiency of glutamate in the body (Jacquet et al. 2005). This metabolic failure leads to various clinical consequences like intellectual disability (ID), kidney failure, seizures, psychiatric problems or other neurological phenotypes (Campbell et al. 1997). The investigators also found that a strain of mouse deficient in Prodh activity exhibited deficits in pre-pulse inhibition of startle, a physiological trait often impaired in patients with schizophrenia (Gogos et al. 1999).

HGMD database has enlisted 24 missense/nonsense mutations that are involved in impaired activity of proline dehydrogenase enzyme. Based on the level of reduction in enzyme activity, these mutations are divided into mild (> 30% reduced enzymatic activity), moderate (> 50% reduced enzymatic activity) and severe (> 70% reduced enzymatic activity) mutations (Bender et al. 2005; Guilmatre et al. 2010; Jang et al. 2013). However, the investigators have also reported a missense mutation (Gln521Arg) that enhance the activity of enzyme (> 120%) (Bender et al. 2005). In the current study, we tried to investigate the structural and functional impact of all reported mutations in *PRODH* and relate it with enzymatic activity of proline dehydrogenase. At position 521, PRODH-203 transcript had 521Arg and PRODH-215 transcript had 521Gln amino acid. So both are the natural variants of PRODH protein, while enhanced enzymatic activity due to this substitution, may be due to substitution of neutral amino acid (Gln) with positively charged amino acid (Arg).Which enhance the binding efficiency of protein with substrate proline. Q19Term mutations was severely reducing the activity of the enzyme due to short truncated premature protein. All other PRODH mutations showed variable degrees of results in 3D structures and binding to its substrate proline. The description of all reported mutations in *PRODH* and their documented effect on the activity of proline dehydrogenase enzyme is summarized in table (1 & 2).Our results also supported the study of Jacquet et al. (2002) that it is difficult to individually estimate the impact of *PRODH* mutations and their effect on the activity of proline dehydrogenase enzyme, because in most cases the individual with abnormal plasma proline levels are not simply homozygotes for a single deleterious mutation or compound heterozygotes, but may carry clusters of several protein variants, and each of them contribute collectively in the enzyme activity (Jacquet et al. 2002). As previously noted, several individuals bearing a potentially deleterious genotype had only mild hyperprolinemia with benign phenotypes because it seems unlikely that such a slight increase in proline level is sufficient to produce a detrimental effect (Hawkins et al. 2006).To confirm the finding of previous studies, we predicted the 3D models of mutation Thr466Met + Thr466Met/Arg453Cys and Leu441Pro + Leu441Pro/Arg453Cys (Hu et al. 2014; Jacquet et al. 2002) and docked them with proline molecule and found that these collective mutations further reduced the activity of PRODH protein to bind to its substrate proline as compared to all single mutated PRODH proteins. Also protein-protein interaction of mutation Thr466Met + Thr466Met/Arg453Cys with close functional interactor ALDH4A1 protein was also reduced as compared to mutation Thr466Met and Arg453Cys solely (Afenjar et al. 2007). So, we suggest that most of the time single deleterious homozygous mutation is not enough to cause a disease phenotype, it may require other heterozygous mutation and/or mutations to show their deleterious effect on enzyme activity.

Conclusion

In brief, we observed that nature of amino acid substitution and number of bonds affect the binding of proline molecule with proline dehydrogenase enzyme and hence affect its activity. In addition to the nature of mutation, we have also observed that the severity in loss of proline hydrogenase function depends on the number of mutations that appear in a single protein, i.e. the more the number of mutation per protein the more will be the severity.

Declarations

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Ethics approval and consent to participate

The present study involved computational analysis of published mutations in *PRODH* and did not enrolled patients, hence exempted from ethical approval.

Competing interests

None declare by all authors

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Author’s Contribution

MM, SWA & AAA performed computational data analysis and drafting of manuscript. MAK conceptualized and supervised the study and remained involved in manuscript drafting & proof read. All authors have read, edited and approved the final version of manuscript.

Data availability Statement:

The computational data is stored in the password protected personal computers of MM and MAK, which is available to editor upon request.

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Figures

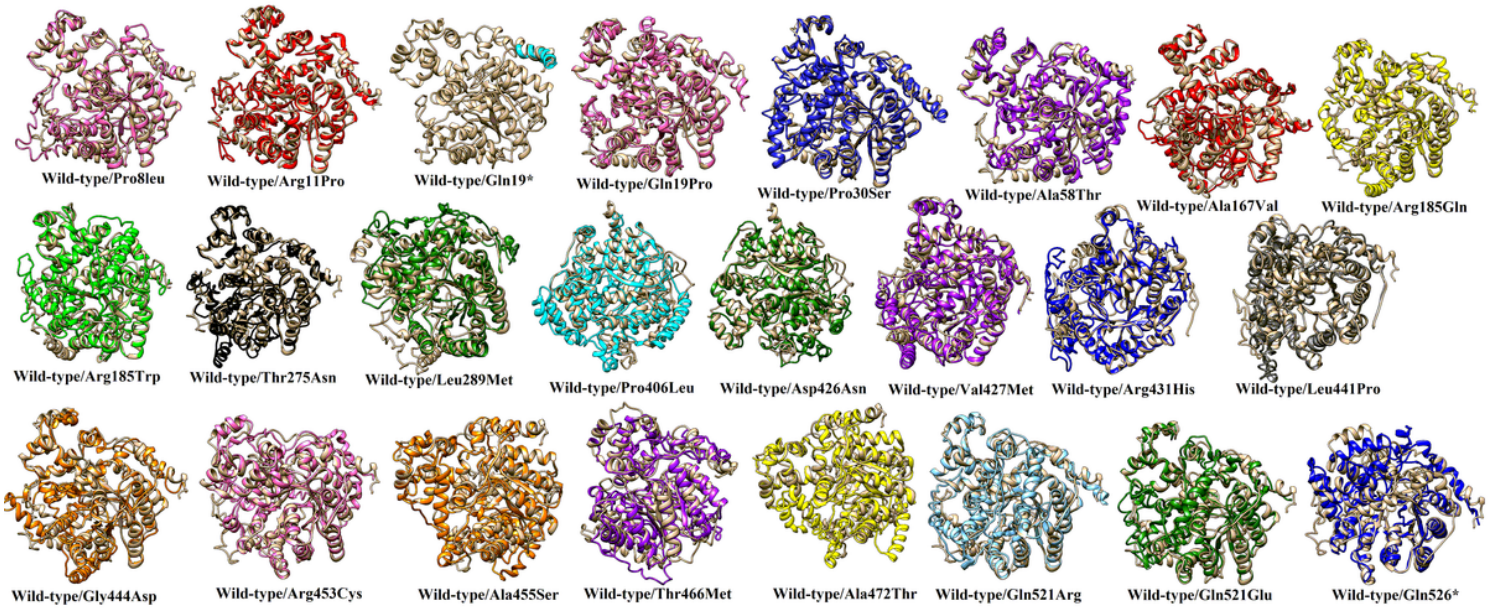

Figure 1

The superimposed 3D images of wildtype PRODH protein with all reported mutant proteins

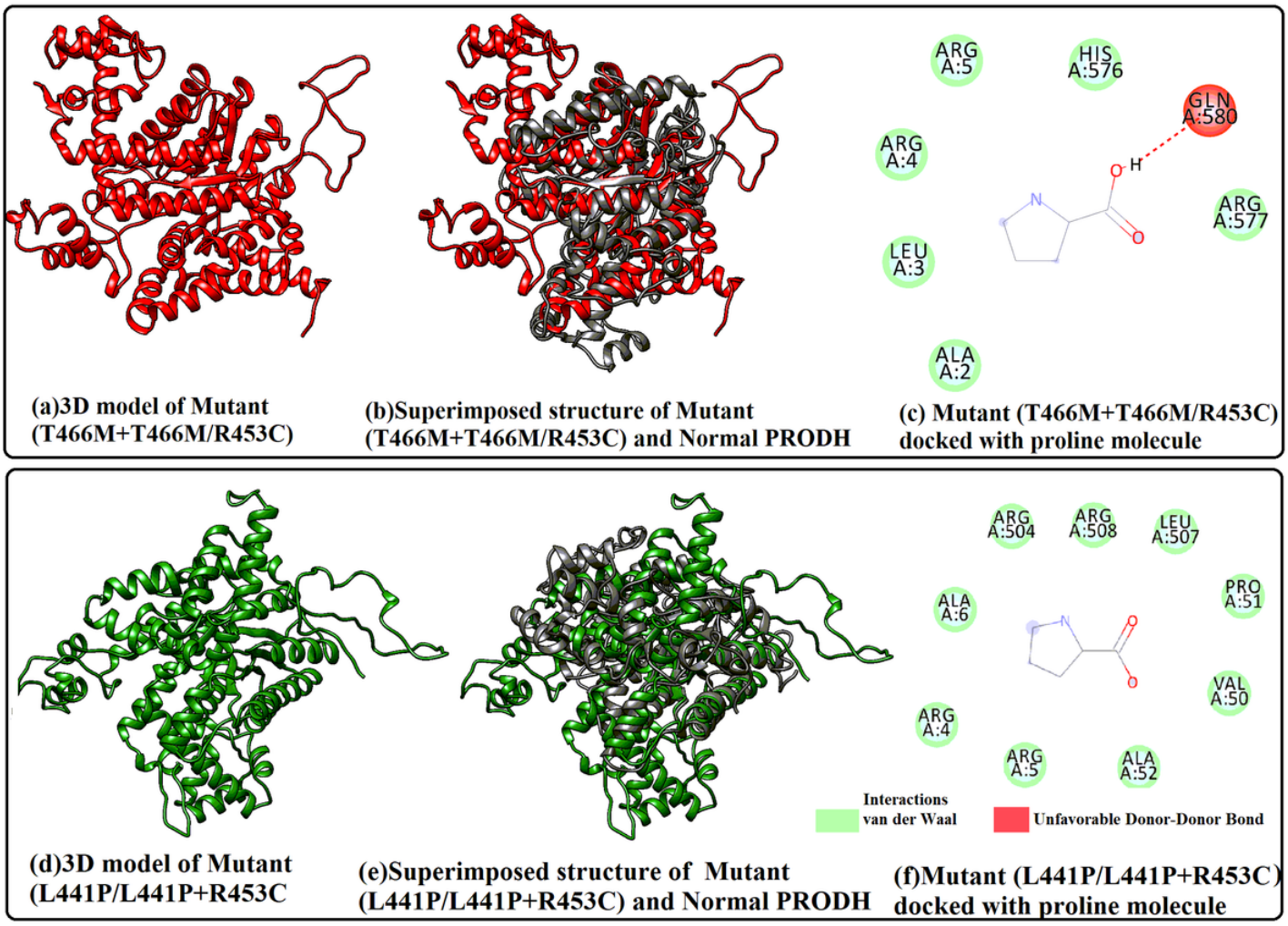

Figure 2

(a) 3D model of compound mutant (T466M+T466M/R453C) protein (b) Superimposed structure of compound mutant (T466M+T466M/R453C) with normal PRODH protein (c) 2D model of mutant (T466M+T466M/R453C) protein docked with proline molecule (d) 3D model of compound mutant (L441P+L441P/R453C) protein (b) Superimposed structure of compound mutant (L441P+L441P/R453C) with normal PRODH protein (c) 2D model of mutant (L441P+L441P/R453C) protein docked with proline molecule

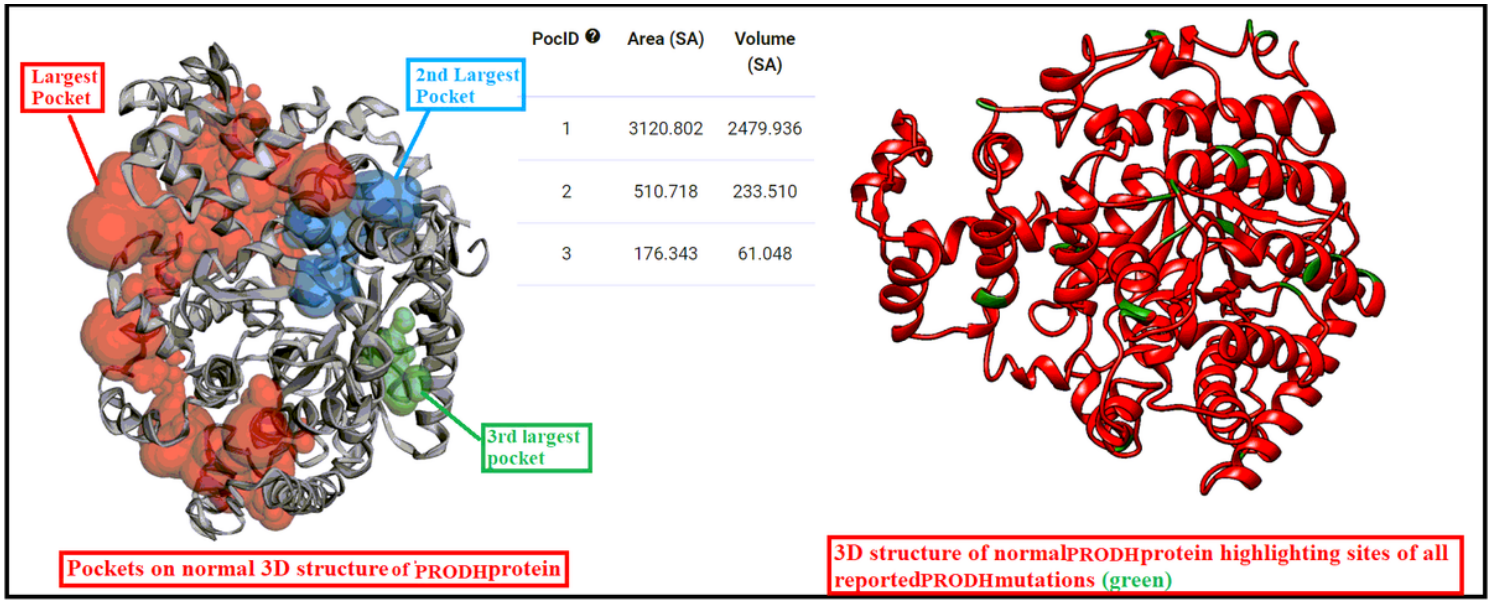

Figure 3

(a) 3D structure of PRODH protein showing predicted active site pocket (b) 3D structure of normal PRODH protein highlighting site of mutation in green colour.

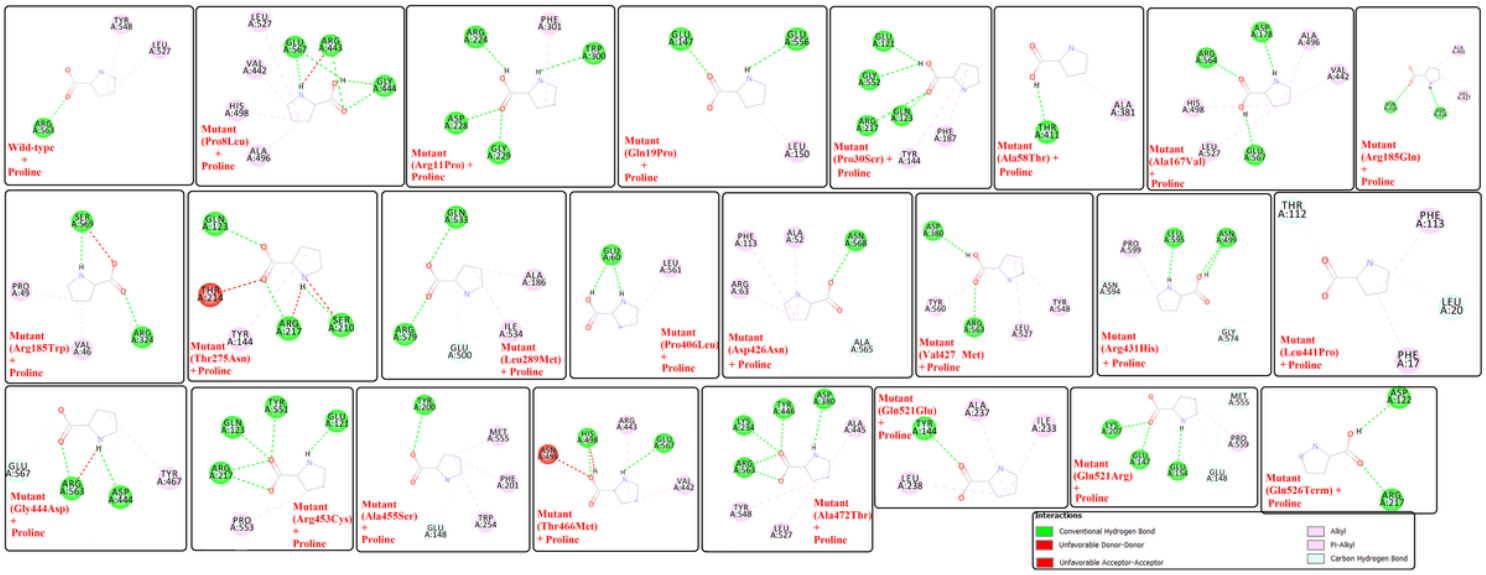

Figure 4

2D illustration of all protein-substrate interaction between wild-type and mutant PRODH protein with proline molecule

Supplementary Files

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