In silico Analysis of Candidate Genes Involved in Sanfilippo Syndrome

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Abstract: *Sanfilippo syndrome is an autosomal recessive lysosomal storage disorder, caused by the deficiency of enzymes that play an important role in degradation of glycosaminoglycans and also called mucopolysaccharidosis III. Mucopolysaccharidosis is genetic disorder. Here, we searched the candidate genes for Sanfilippo syndrome by using BLAST with the query sequence. As no suitable homology was found against the query sequence we moved towards threading approach. The threading approach was carried out by employing online CPH models and LOMETS tools. Through present research, domains of the proteins were predicted by utilizing the Domain Sweep tools, GNS and two domains were reported. Motif search reported the maximum number of motifs for Type D protein as compared to other types. All four proteins were totally soluble proteins and no transmembrane domains were found. In future, these results and predicted 3D structures can be used for the molecular docking studies, binding activities and protein-protein interactions for all the four types of Sanfilippo syndrome.*

Keywords: *Mucopolysaccharidosis, Sanfilippo syndrome, Structure prediction, Bioinformatics.*

Introduction

Sanfilippo syndrome also called mucopolysaccharidosis (MPS) III is the only syndrome among the MPS syndromes which does not contain any animal counterpart yet, whereas all other types of MPS contain animal counterparts. Numerous research work evidenced that caprine MPS HID is suitable animal model for investigating Sanfilippo syndrome and for the therapeutic strategies [11].

Sanfilippo syndrome is an autosomal recessive lysosomal storage disorder caused by the deficiency of enzymes that play an important role in degradation of glycosaminoglycans (GAGs). The deficiency of these enzymes leads to the accumulation of MPS in different cells of the body that cause damage to surrounding organs and tissues [9].

In MPS III, four enzymes deficiency occurs for each type. It was found that GAGs mostly gets accumulated in the brain was Heparan sulphate, a complex polymer having glucosamine and N-acetyl glucosamine residues. It is located in the extracellular matrix [17]. The MPS are complex sugars, so deficiency of a specific enzyme to breakdown of complex sugar takes place and get accumulated in the tissues and organs, resulted in disease. Although the enzyme

for each type is different but at the end heparan sulphate is excreted and get accumulated in greater amount due to the deficiency of a specific enzyme [7].

The typical manifestations of Sanfilippo syndrome begin with aggressive behavior, sleep disorders, hyperactivity and delayed development. Due to the progression of dementia, Sanfilippo patients become quite withdrawn and eventually loose contact with their surrounding environment [5]. Hearing loss is also common among them [1].

The Sanfilippo syndrome belongs to a family of disorders lysosomal storage diseases, and historically as the MPS. Four distinct subtypes of Sanfilippo syndrome have been described such as Sanfilippo syndrome A, Sanfilippo syndrome B, Sanfilippo syndrome C, Sanfilippo syndrome D. All of these disorders are characterized by the lysosomal accumulation and excretion of undegraded GAGs as a consequence of deficiencies in lysosomal hydrolases. The biochemical basis for each of the four types of Sanfilippo syndrome have distinction but their clinical presentations are quite similar [15, 21].

Sanfilippo type A is the most severe form of the disease exhibiting the earliest onset, most rapid progression of symptoms and shorter survival. The most common symptom among the entire Sanfilippo syndrome's type is central nervous system deterioration. It has great effect on musculoskeletal system but still not severe as in other MPS types [21]. A progressive neurological deterioration with severe mental retardation begins in childhood and includes aphasia, vasomotor instability, epilepsy, and dementia [7]. All the patients suffering from MPS III needs early treatment as it becomes severe with the passage of time. Patients may suffer through severe neurological manifestations which can be proved very devastating as the time passes. MPS III has strong effect on mind, speech and behavior. Diarrhea and epilepsy are also common among these patients [8].

These subtypes contain enzymes that help in degradation of heparan sulphate. All these types have different enzymes but perform the same function of degradation of heparan sulphate. Among all types, Sanfilippo syndrome A is the most common and different from all other types of MPS as it is also involved in cardiac disorders [12, 13].

Recent studies have shown that four different substrates had been made for each of the four types of Sanfilippo syndrome. This study evidenced that these substrates can accurately detect the syndrome in fibroblast lysates. It was also observed in unaffected patients that enzyme activity got lower by the factor of 10 [22].

The present study was focused on functional analysis, secondary and tertiary structure prediction of the genes involved in Sanfilippo syndrome through different bioinformatics tool. Various significant domains were also identified in this study.

Secondary structure prediction is important as it is preliminary for tertiary structure prediction. Secondary structure is formed by alpha helixes and beta sheets. Some proteins have greater tendency to form alpha helixes and some have greater tendency to form beta sheets. Tahir et al. [23, 24] applied methodology that was utilized to predict the three dimensional structure of protein for reliable comparative modeling analysis. In future, these results and predicted 3D structures can be used for the molecular docking studies, binding activities and protein-protein interactions of all four types of Sanfilippo syndrome. These findings can also be further useful in drug designing.

Materials and methods

Protein sequences of GNS, SGSH, NAGLU and HGSNAT with accession number B4DTT0, B7Z9A6, H0Y2D8, Q96ED6 respectively were retrieved from Uniprot Knowledgebase in FASTA format. To evaluate the amino acid residues, molecular weight, Isoelectric point, charge and localized protein predictions ProtSweep was used [19].

Functional analysis of the protein includes prediction of domains, interactions between domains and motifs. Domain Sweep utilized for domains identification [19].

PROSITE, BLOCKS, PRINTS, ProDom were determined through Motif search [28].

SABLE is accurate sequence-based prediction of relative solvent accessibilities, secondary structures and transmembrane domains for proteins of unknown structure [27]. SABLE examined the secondary structures of proteins from their amino acid sequences.

For tertiary structure prediction Protein-Protein BLAST (PSI-BLAST) [26] was chosen for similarity search but due to unavailability of suitable templates threading approach was utilized for homology modeling. This method is also known as remote homology method.

For threading method, online threading servers CPH models and LOMETS were employed. CPH models is a threading server, searched templates and generated one model for each of the type of protein involved in Sanfilippo syndrome [29]. LOMETS tool also utilized and generated ten best models for each of the protein involved in Sanfilippo syndrome types [25].

ERRAT [3], RAMPAGE [14] and VERIFY3D [4] were used for assessment of protein structures. A plot obtained from the VERIFY3D represented the average 3D-1D profile score.

Protein models were further evaluated on the basis of statistics of chemical interactions of proteins and the Ramachandran kinemage created by MolProbity server [2]. The protein structures were analyzed by RASMOL [18] visualization tool.

Results and discussion

MPS is caused by the accumulation of GAGs. Eleven different types of enzymes are involved in the degradation of GAGs. The deficiency occurs in these enzymes results to any one type of MPS. Sanfilippo syndrome, one of the types of MPS is an autosomal recessive lysosomal storage disorder which is involved in the deficiency of enzymes that play an important role in degradation of GAGs [9].

The proteins involved in Sanfilippo syndrome has been selected for homology modeling because experimentally 3D structure were not predicted yet as per literature survey and PDB. To predict 3D structure from sequence is a task challenging enough to have occupied a generation of researchers. We predicted the 3D structure for all the four proteins involved in Sanfilippo syndrome through threading technique and obtained optimized results for all the four types of proteins. Through present research, domains of the proteins were predicted by using the Domain Sweep tools, GNS reported two domains and also reported two patterns in PROSITE database showing Sulphatase as a family and Alkaline Sulphatase as a Superfamily. Motif search reported the maximum number of motifs for Type D protein GNS in Prodom, PRINTS, Pfam and PROSITE databases as compared to SGSH, NAGLU and HGSNAT proteins. All four proteins were totally soluble proteins and no transmembrane

domains were found in it. The secondary structure showed that GNS (B4DTT0) reported the highest number of beta strands and coil regions.

Tertiary structures of proteins have been generated by CPH models and LOMETS, which showed satisfactory coverage. Ten different models were generated and the models having least energy were selected. Various tools were employed and results were analyzed. The results obtained through predicted models were optimized except RAMPAGE for which > 80% region was preferred to be the best model as shown in example Table 1.

Table 1. RAMPAGE evaluation analyses of models (3B5Q.A-B7Z9A6, 2VCA.A-H0Y3D8, 3A2KA1-Q96ED6 and 3B5Q.B-B4DTT0)

Sr. No.	No. of residues	3B5Q.A-B7Z9A6	2VCA.A-H0Y3D8	3A2KA1-Q96ED6	3B5Q.B-B4DTT0
1	Favored region	329 (86.1%)	108 (87.1%)	321 (92.0%)	53 (82.8%)
2	Allowed region	38 (9.9%)	8 (6.5%)	20 (5.7%)	7 (10.9%)
3	Outlier region	15 (3.9%)	8 (6.5%)	8 (2.3%)	4 (6.2%)

Ramachandran plot calculated favored regions, allowed regions and outlier regions for all the four models of B7Z9A6, H0Y3D8, Q96ED6 and B4DTT0 sequences as depicted in Table 1. ERRAT calculated the overall quality factor by plotting a graph. Good high resolution structures generally produce values around 95% but maximum overall quality factor was 89.796 for 3B5Q.A-B7Z9A6 model, 99.118 for 2VCA.A-H0Y3D8 model, 62.712 for 3A2KA1-Q96ED6 model and 79.718 for 3B5Q.B-B4DTT0 model. COLORADO 3D was the tool used for the evaluation of average score for all the models. The average score lowest range was set as 0.0 and highest range was set as 0.4 so the score touching the range 0.4 was considered as the best score and 0.4 was evaluated for 2VCA.A-H0Y3D8 and 3B5Q.B-B4DTT0 protein sequences only. Evaluation parameters and values calculated are reported in Tables 2-5.

Table 2. Predicted structure of B7Z9A6 and 3B5Q.A selected on the basis of different tools

Sr. No.	Tools used	CPH and LOMETS	ERRAT	RAMPAGE	Colorado 3D (VERIFY3D)	MolProbity
	Parameters	Z score	Overall quality factor	Favored region	Average score	Cβ deviations > 0.25Å
1	**3B5Q.A**	**10.8**	**89.796**	**82.8%**	**0.0**	**0**
2	3gv2A	4.136	70.256	90.6%	0.0	4
3	2jl6J	3.414	8.235	72.9%	0.0	11
4	3sqlA	9.522	15.385	87.2%	0.0	1
5	1fcq_A	5.992	30.178	91.1%	0.0	1
6	2q41A2	4.168	43.147	88.2%	0.02	1
7	2p1oB1	5.772	43.655	88.7%	0.05	3
8	2q41A2	4.168	43.147	88.2%	0.02	1
9	2q41A2	4.168	43.147	88.2%	0.02	1
10	2ebo_A	5.090	49.573	90.1%	0.0	0
11	3lwtX2	8.060	31.481	94.1%	0.0	0

Table 3. Predicted structures of H0Y3D8 and 2VCA.A selected on the basis of different tools

Sr. No.	Tools used	CPH and LOMETS	ERRAT	RAMPAGE	Colorado 3D (VERIFY3D)	MolProbity
	Parameters	Z score	Overall quality factor	Favored region	Average score	Cβ deviations > 0.25Å
1	**2VCA.A**	**56.0**	**99.118**	**92.0%**	**0.4**	**0**
2	2vcaA	18.272	67.317	91.6%	0.05	5
3	2vcaA	150.089	68.370	91.8%	0.18	7
4	2vc9A	12.504	69.100	91.1%	0.0	9
5	2vcaA3	36.696	72.266	94.7%	0.31	2
6	2vcaA	18.272	67.317	91.6%	0.05	5
7	2vcaA	18.272	67.317	91.6%	0.05	5
8	2vcaA3	8.581	66.802	94.5%	0.18	3
9	2vcc_A	12.917	70.488	91.6%	0.0	11
10	2vcaA3	8.581	66.802	94.5%	0.18	3
11	1qsaa1	4.789	69.250	95.4%	0.0	2

Table 4. Predicted structures of Q96ED6 and 3a2kA1 selected on the basis of different tools

Sr. No.	Tools used	CPH and LOMETS	ERRAT	RAMPAGE	Colorado 3D (VERIFY3D)	MolProbity
	Parameters	Z score	Overall quality factor	Favored region	Average score	Cβ deviations > 0.25Å
1	1CGD.A	6.1	Not calculated	100.0%	0.12	0
2	2vg8A1	4.471	37.288	88.7%	0.01	1
3	1wa7_B	8.312	3.488	96.8%	0.0	0
4	1jvrA	5.564	33.898	87.9%	0.0	4
5	1jvrA	8.684	49.153	90.3%	0.0	5
6	2vg8A3	4.838	17.797	89.5%	0.23	0
7	1jvrA	5.564	33.898	87.9%	0.0	4
8	1jvrA	5.564	33.898	87.9%	0.0	4
9	**3a2kA1**	**9.247**	**62.712**	**87.1%**	**0.22**	**7**
10	2jl6J	2.362	8.475	79.0%	0.0	6
11	1w5q_A	7.279	10.169	90.3%	0.0	1

In MolProbity, one best model was selected on the basis of Cβ deviations > 0.25Å for all four proteins and also by analyzing the favored regions shown by the Ramachandran plots [16]. Goal for Cβ deviations was 0 for a model to be considered as best model. The Cβ deviation was 0 for 3B5Q.A-B7Z9A6, 3B5Q.B-B4DTT0 and 2VCA.A-H0Y3D8.

On the basis of certain parameters, taken from the evaluation tools such as highest Z score, greater overall quality factor, greater favored region, average score and Cβ deviations > 0.25Å, which showed the highest value among these models the best model was selected as shown in Figs. 1-4.

Table 5. Predicted structures of B4DTT0 and 3B5Q.B selected on the basis of different tools

Sr. No.	Tools used	CPH and LOMETS	ERRAT	RAMPAGE	Colorado 3D (VERIFY3D)	MolProbity
	Parameters	Z score	Overall quality factor	Favored region	Average score	Cβ deviations > 0.25Å
1	**3B5Q.B**	**54.8**	**79.718**	**86.1%**	**0.4**	**0**
2	3ed4B	12.997	32.321	91.4%	0.0	10
3	3ed4B	72.941	25.455	87.6%	0.0	24
4	1hdh_A	45.025	39.732	93.6%	0.0	3
5	2vqrA	14.668	31.670	91.0%	0.0	2
6	2vqrA	33.574	33.781	93.6%	0.0	2
7	2vqrA	13.774	33.259	92.9%	0.0	4
8	3b5qB	13.190	27.233	86.9%	0.0	12
9	2vqrA	13.774	33.259	92.9%	0.0	4
10	2vqrA	13.774	33.259	92.9%	0.0	4
11	1hdhA1	50.882	34.870	92.1%	0.0	6

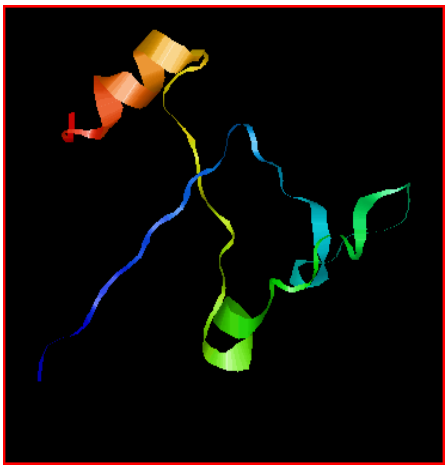

Fig. 1 3D structure of B7Z9A6
3B5Q.A-B7Z9A

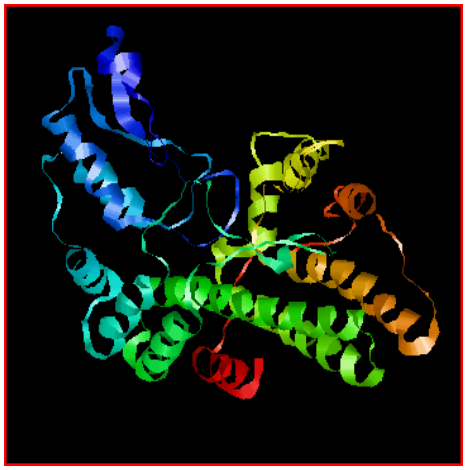

Fig. 2 3D structure of H0Y3D8
2VCA.A-H0Y4D8

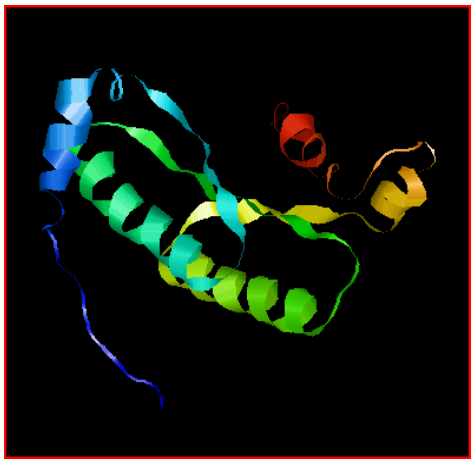

Fig. 3 3D structure of Q96ED6
3a2kA1-Q96ED6

Fig. 4 3D structure of B4DTT0
3B5Q.B-B4DTT0

Conclusion

Sanfilippo syndrome is an autosomal recessive lysosomal storage disorder caused by the deficiency of enzymes that play an important role in degradation of GAGs. The proteins involved in Sanfilippo syndrome has been selected for homology modeling because experimentally 3D structure were not predicted yet as per literature survey and PDB. Currently, no effective therapy is yet available for this disease so in order to have better therapeutic strategies or to manufacture new treatments it is crucial to predict the structure of a protein through post translational modification, domains identification and predicting secondary and tertiary structures. The secondary structure showed that GNS (B4DTT0) reported the highest number of beta strands and coil regions. Tertiary structures of proteins have been generated by CPH models and LOMETS, which showed satisfactory coverage. Finding 3D structure would further help researchers to work on drug designing and simulations, regarding the genes involved in Sanfilippo syndrome.

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