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In silico structure based molecular expression and modeling of PTEN gene for proteus syndrome

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ABSTRACT

Proteus syndrome is a very complex and rare to find in world. It consists asymmetric and disproportionate overgrowth in bones and skins. There are very few cases that have been come in light all over the world such as 1 over 1 million. The drug designing is the inventive process of finding new medications based on the knowledge of a biological target. It also involves the design of small molecules that are complementary in shape and charge to the bimolecular target with which they interact and therefore will bind to it. Proteus syndrome is caused by AKT1 and PTEN genes. The PTEN gene is taken for the modeling and research. It consists 403 amino acids and it acts as a tumor suppressor. Proteus syndrome is not a disease but a disorder. It is related to the PI3K-AKT Signaling Pathway which eventually led to the clinical approaches as their effect. So that, the structure based molecular expression and modeling can be taken to a direction and lead to the mainly drug designing for the welfare of the suffering persons of this syndrome.

Key Words: Proteus Syndrome, PTEN

INTRODUCTION

Proteus syndrome is a very complex and rare to find in the world. It consists asymmetric and disproportionate overgrowth in bones and skins. There are very few cases that have been come in light all over the world. The responsible genes for the proteus syndrome were AKT1 gene and PTEN. AKT1 is causing of proliferation, growth in cell cycle and PTEN is tumor suppressor gene in which the change causes the growth in cells. Proteus syndrome is a mutation occurs in chromosomes and it is a disorder not a disease. The major breaks of pathway are commonly found and eventually lead

to the clinical approaches as their effect (1). Sir Frederick Treves first showed Joseph Merrick, the famous elephant man, to the Pathological society of London in 1884. A diagnosis of neurofibromatosis was suggested in 1909. Evidence indicates that Proteus syndrome is a rare condition that involves atypical growth of the bones, skin and head and a variety of other symptoms. The syndrome has multiple, diverse, somatic manifestations that evolve over time and involve the skeletal system, soft tissues, skin, and vascular system. These signs include partial gigantism of the hands and/or feet, asymmetry of the limbs, plantar hyperplasia, macrodactyly, bony exostoses, soft-tissue tumors (hemangioma, lymphangioma, and lipoma), varicosities, verrucous epidermal nevi, and long bone overgrowth. It may affect tissues derived from any of the three germinal layers. It is caused by abnormal AKT1 gene or PTEN gene due to mutation of chromosome 10 or 16. Proteus syndrome is a complex disorder first described by the Cohen and Hayden in 1997 (2). Weidman et al in 1983 give this condition after the Greek God Proteus, the polymorphous, who will able to change his bodily, shape and form to his will. The syndrome has multiple, diverse, somatic manifestations that evolve over time and involve the skeletal system, soft tissues, skin, and vascular system (3). Proteus syndrome (PS) is an extremely rare and over diagnosed disorder of mosaic growth deregulations, primarily involving overgrowth. The disorder is thought to be caused by a somatic genetic alteration but the etiology is unknown. Clinical diagnosis of PS is challenging and controversial. The management of PS is also challenging, primarily owing to the aggressive and disproportionate postnatal overgrowth. Patients with PS have an increased risk of premature death, commonly caused by deep venous thrombosis and pulmonary embolism. Patients with PS have an increased risk of developing tumors. These signs include partial gigantism of the hands and/or feet, asymmetry of the limbs, plantar hyperplasia, macrodactyly, bony exostoses, soft-tissue tumors (hemangioma, lymphangioma, and lipoma), varicosities, verrucous epidermal nevi, and long-bone overgrowth (4). Homology modeling, also known as comparative modeling of protein, refers to constructing an atomic-resolution model of the "target" protein from its amino acid sequence and an experimental three-dimensional structure of a related homologous protein (the "template"). Homology modeling relies on the identification of one or more known protein structures likely to resemble the structure of the query sequence, and on the production of an alignment that maps residues in the query sequence to residues in the template sequence. It has been shown that protein structures are more conserved than protein sequences amongst homologues, but sequences falling below a 20% sequence identity can have very different structure (5). Evolutionarily related proteins have similar sequences and naturally occurring homologous proteins have similar protein structure. It has been shown that three-dimensional protein structure is evolutionarily more conserved than would be expected on the basis of sequence conservation alone. (6). the sequence alignment and template structure are then used to produce a structural model of the target. Because protein structures are more conserved than DNA sequences, detectable levels of sequence similarity usually imply significant structural similarity (7). The quality of the homology model is dependent on the quality of the sequence alignment and template structure. The approach can be complicated by the presence of alignment gaps (commonly called indels) that indicate a structural region present in the target but not in the template, and by structure gaps in the template that arise from poor resolution in the experimental procedure (usually X-ray crystallography) used to solve the structure. Model quality declines with decreasing sequence identity; a typical model has ~1–2 Å root mean square deviation between the matched C^{α} atoms at 70% sequence identity but only 2–4 Å agreement at 25% sequence identity. However, the errors are significantly higher in the loop regions, where the amino acid sequences of the target and template proteins may be completely different. Regions of the model that were constructed without a template, usually by loop modeling, are generally much less accurate than the rest of the model. Errors in side chain packing and position also increase with decreasing identity, and variations in these packing configurations have been suggested as a major reason for poor model quality at low identity (8). Taken together, these various atomic-position errors are significant and impede the use of homology models for purposes that require atomic-resolution data, such as drug design and protein–protein interaction predictions; even the quaternary structure of a protein may be difficult to predict from homology models of its subunit(s).

Nevertheless, homology models can be useful in reaching qualitative conclusions about the biochemistry of the query sequence, especially in formulating hypotheses about why certain residues are conserved, which may in turn lead to experiments to test those hypotheses. For example, the spatial arrangement of conserved residues may suggest whether a particular residue is conserved to stabilize the folding, to participate in binding some small molecule, or to foster association with another protein or nucleic acid. Homology modeling can produce high-quality structural models when the target and template are closely related, which has inspired the formation of structural genomics consortium dedicated to the production of representative experimental structures for all classes of protein folds (9). The chief inaccuracies in homology modeling, which worsen with lower sequence identity, derive from errors in the initial sequence alignment and from improper template selection (10). Like other methods of structure prediction, current practice in homology modeling is assessed in a biennial large-scale experiment known as the Critical Assessment of Techniques for Protein Structure Prediction, or CASP. Clustering algorithms are used to organize this expression data into different biologically relevant clusters. We can then compare the expression profiles from the diseased and healthy cells to help us understand the role our gene or protein plays in a disease process. All of these computational tools can help to compose a detailed picture about a protein family, its involvement in a disease process and its potential as a possible drug target. Following on from the genomics explosion and the huge increase in the number of potential drug targets, there has been a move from the classical linear approach of drug discovery to a non linear and high throughput approach. The field of bioinformatics has become a major part of the drug discovery pipeline playing a key role for validating drug targets. By integrating data from many inter-related yet heterogeneous resources, bioinformatics can help in our understanding of complex biological processes and help improve drug discovery (11).

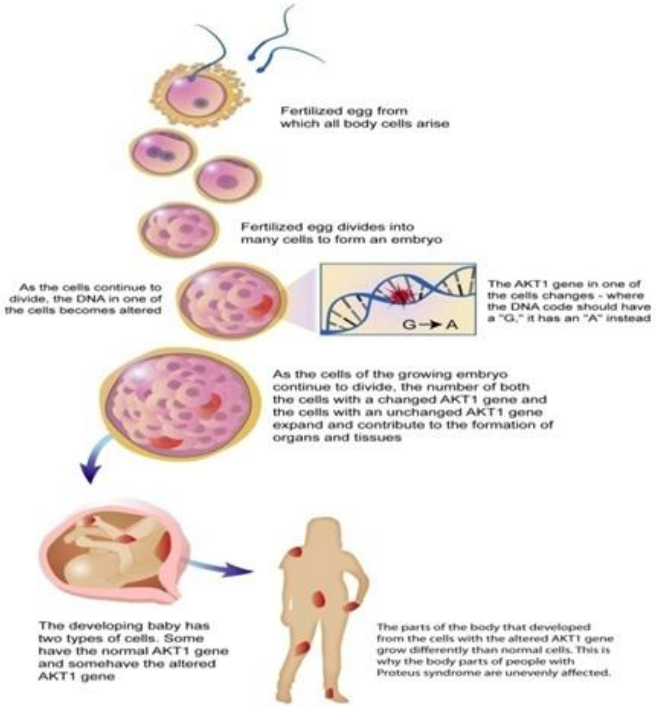


Figure1: AKT1 gene regulation in human.

Phosphatase and tensin homolog (PTEN) is a protein that, in humans, is encoded by the PTEN gene. Mutations of this gene are a step in the development of many cancers. PTEN acts as a tumor suppressor gene through the action of its phosphatase protein product. This phosphatase is involved in the regulation of the cell cycle, preventing cells from growing and dividing too rapidly. (OrthoMam phylogenetic marker: PTEN coding sequence)It is one of the targets for drug candidates such as the oncomiR, MIRN21. This gene was identified as a tumor suppressor that is mutated in a large number of cancers at high frequency. The protein encoded by this gene is a

phosphatidylinositol-3, 4, 5-trisphosphate 3-phosphatase. It contains a tensin-like domain as well as a catalytic domain similar to that of the dual specificity protein tyrosine phosphatases. Unlike most of the protein tyrosine phosphatases, this protein preferentially dephosphorylates phosphoinositide substrates. It negatively regulates intracellular levels of phosphatidylinositol-3, 4, 5-trisphosphate in cells and functions as a tumor suppressor by negatively regulating akt/pten signaling pathway (12). The corresponding PTEN protein is found in almost all tissues in the body. PTEN protein acts as a phosphatase to dephosphorylate phosphatidylinositol (3, 4, 5)-trisphosphate (PtdIns (3, 4, 5)P_3 or PIP_3). PTEN specifically catalyses the dephosporylation of the 3` phosphate of the inositol ring in PIP_3, resulting in the biphosphate product PIP_2 (PtdIns(4,5) P2). This dephosphorylation is important because it results in inhibition of the AKT signaling pathway. The structure of PTEN (solved by X-ray crystallography) reveals that it consists of a phosphate domain, and a C2 domain: the phosphatase domain contains the active site, which carries out the enzymatic function of the protein, while the C2 domain binds the phospholipid membrane. Thus PTEN binds the membrane through its C2 domain, bringing the active site to the membrane-bound PIP_3 to de-phosphorylate it. When the PTEN enzyme is functioning properly, it acts as part of a chemical pathway that signals cells to stop dividing and can cause cells to undergo programmed cell death (apoptosis) when necessary. These functions prevent uncontrolled cell growth that can lead to the formation of tumors. There is also evidence that the protein made by the PTEN gene may play a role in cell movement (migration) and adhesion of cells to surrounding tissues. PTEN orthologus have been identified in most mammals for which complete genome data are available. Tumor suppressor Acts as a dual-specificity protein phosphatase, dephosphorylating tyrosine-, serine- and threonine-phosphorylated proteins Also acts as a lipid phosphatase, removing the phosphate in the D3 position of the inositol ring from phosphatidylinositol 3,4,5-trisphosphate, phosphatidylinositol 3,4-diphosphate, phosphatidylinositol 3-phosphate and inositol 1,3,4,5-tetrakisphosphate with order of substrate preference in vitro PtdIns(3,4,5)P3 > PtdIns(3,4)P2 > PtdIns3P > Ins(1,3,4,5)P4. The lipid phosphatase activity is critical for its tumor suppressor function. Antagonizes the PI3K-AKT/PKB signaling pathway by dephosphorylating phosphoinositides and thereby modulating cell cycle progression and cell survival The unphosphorylated form cooperates with AIP1 to suppress AKT1 activation. Dephosphorylates tyrosine-phosphorylated focal adhesion kinase and inhibits cell migration and integrin-mediated cell spreading and focal adhesion formation. Plays a role as a key modulator of the AKT-mTOR signaling pathway controlling the tempo of the process of newborn neurons integration during adult neurogenesis, including correct neuron positioning, dendritic development and synapse formation May be a negative regulator of insulin signaling and glucose metabolism in adipose tissue The nuclear monoubiquitinated form possesses greater apoptotic potential, whereas the cytoplasmic nonubiquitinated form induces less tumor suppressive ability. In motile cells, suppresses the formation of lateral pseudopods and thereby promotes cell polarization and directed movement (13-15).

CLINICAL SIGNIFICANCE

CANCER

PTEN is one of the most commonly lost tumor suppressors in human cancer; in fact, up to 70% of men with prostate cancer are estimated to have lost a copy of the PTEN gene at the time of diagnosis. During tumor development, mutations and deletions of PTEN occur that inactivate its enzymatic activity leading to increased cell proliferation and reduced cell death. Frequent genetic inactivation of PTEN occurs in glioblastoma, endometrial cancer, and prostate cancer; and reduced expression is found in many other tumor types such as lung and breast cancer. Furthermore, PTEN mutation also causes a variety of inherited predispositions to cancer (16).

NON-CANCEROUS NEOPLASIA

Researchers have identified more than 70 mutations in the PTEN gene in people with Cowden syndrome. These mutations can be changes in a small number of base pairs or, in some cases, deletions of a large number of base pairs. Most of these mutations cause the PTEN gene to make a protein that does not function properly or does not work at all. The defective protein is unable to stop cell division or signal abnormal cells to die, which can lead to tumor growth, particularly in the breast, thyroid, or uterus (17-18). Mutations in

the PTEN gene cause several other disorders that, like Cowden syndrome, are characterized by the development of non-cancerous tumors called hamartomas. The defective protein allows the cell to divide in an uncontrolled way and prevents damaged cells from dying, which can lead to the growth of tumors (19).

BRAIN FUNCTION AND AUTISM

Defects of the PTEN gene have been cited to be a potential cause of autism spectrum disorders. When defective, PTEN protein interacts with the protein of a second gene known as Tp53 to dampen energy production in neurons. This severe stress leads to a spike in harmful mitochondrial DNA changes and abnormal levels of energy production in the cerebellum and hippocampus, brain regions critical for social behavior and cognition. When PTEN protein is insufficient, its interaction with p53 triggers deficiencies and defects in other proteins that also have been found in patients with learning disabilities including autism. Patients with defective PTEN can develop cerebellar mass lesions called dysplastic gangliocytomas or Lhermitte–Duclos disease (20-22).

CELL REGENERATION

PTEN's strong link to cell growth inhibition is being studied as a possible therapeutic target in tissues that do not traditionally regenerate in mature animals, such as central neurons. PTEN deletion (genetics) mutants have recently been shown to allow nerve regeneration in mice (23).

TREATMENTS AVAILABLE

Rapamycin is only drug available in the whole world.

Surgury is available (24).

RAPAMYCIN

Rapamycin (also known as Sirolimus) is a chemical that was discovered by Suren Sehgal, as a product of bacteria discovered on Easter Island (the island is also known as Rapa Nui). It was approved by the US food and drug administration in September 1999 and is marketed under the trade name Rapamune by Pfizer. Sirolimus was originally developed as an antifungal agent. However, this use was abandoned when it was discovered to have potent immunosuppressive and antiproliferative properties. It has since been shown to prolong the life of mice and might also be useful in the treatment of certain cancers (25-27).

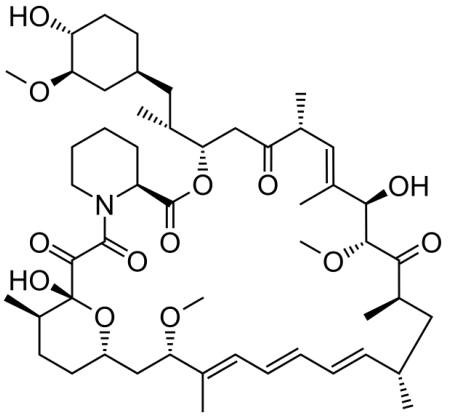


Figure 2: Chemical Structure of Rapamycin

Rapamycin exists as one isomer (structurally homogeneous) in the solid form as indicated by X-rays whereas in solution there are two conformational isomers (approx. 4:1) which exist in equilibrium. Through NMR analysis, the "isomerism is shown to be associated with the trans-cis rotation of an amidic bond within the 31-membered macrolide ring" (28-30).

MATERIALS AND METHODS

In the following paragraphs, I have briefly enlisted the various bioinformatics databases that have been of critical importance in completing my project work. Biological databases are stores of biological information. Most of these databases are "open source" and are open to all the researches worldwide, thus themselves getting constantly updated according to the latest findings and requirements if any: NCBI, GENECARDS, BLAST, PDB, and PubMed (31).

PROTPARAM

ProtParam is a tool which allows the computation of various physical and chemical parameters for a given protein stored in SwissProt or for a user entered sequence. The computed parameters include the molecular weight, theoretical pI, amino acid composition, atomic composition, extinction coefficient, estimated half-life, instability index, aliphatic index and grand average of hydropathicity .ProtParam computes various physico-chemical properties that can be deduced from a protein sequence (32, 33).

SOPMA

SOPMA is a secondary structure prediction method. SOPMA (Self-Optimized Prediction Method with Alignment) is an improvement of SOPM method. These methods are based on the homologue method of Levin et al. SOPMA correctly predicts 69.5% of amino acids for a three-state description of the secondary structure (alpha-helix, beta-sheet and coil) in a whole database containing 126 chains of non-homologous (less than 25% identity) proteins. Joint prediction with SOPMA and a neural networks method (PHD) correctly predicts 82.2% of residues for 74% of co-predicted amino acids (24, 25, 34)

PHYRE

The Phyre automatic fold recognition server for predicting the structure and/or function of your proteinsequence

Phyre and Phyre2 (Protein Homology Analog Y Recognition Engine; pronounced as 'fire') are web-based services for protein structure prediction that are free for non-commercial use. Phyre is among the most popular methods for protein structure prediction having been cited over 1000 times (35, 36).

HH PRED

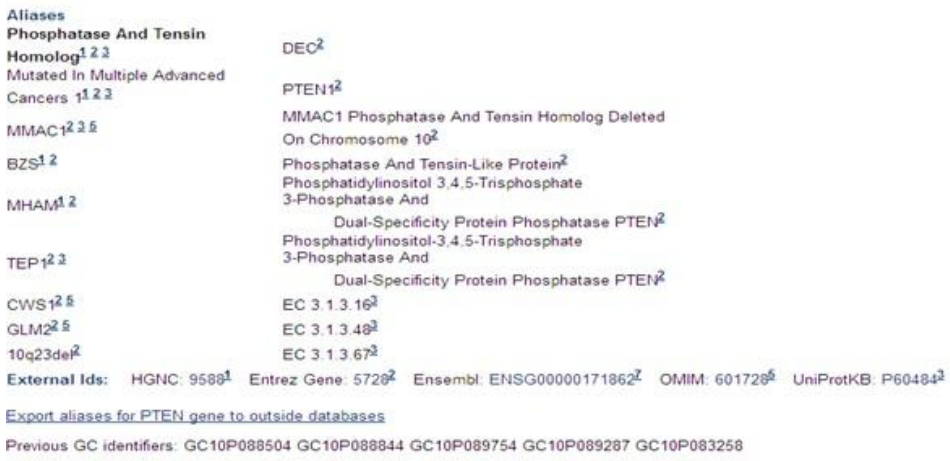
HHsearch is an open-source software program for protein sequence searching that is part of the free HH-suite software package (37). HHpred is a free protein function and protein structure prediction server that is based on HHsearch and HHblits, another program in the HH-suite package (38). HHpred and HH search are among the most popular methods for protein structure prediction and the detection of remotely related sequences, each having been cited over 500 times. The primary aim in developing HHpred was to provide biologists with a method for sequence database searching and structure prediction that is as easy to use as BLAST or PSI-BLAST and that is at the same time much more sensitive in finding remote homologs (39-42).

PROSITE

Prosite is a protein database (43, 44). It consists of entries describing the protein families, domains and functional sites as well as amino acid patterns, signatures, and profiles in them. These are manually curated by a team of the Swiss Institute of Bioinformatics and tightly integrated into Swiss-Prot protein annotation. PROSITE was created in 1988 by Amos Bairoch (45-47)

RESULTS AND DISCUSSION

(A)



(B)

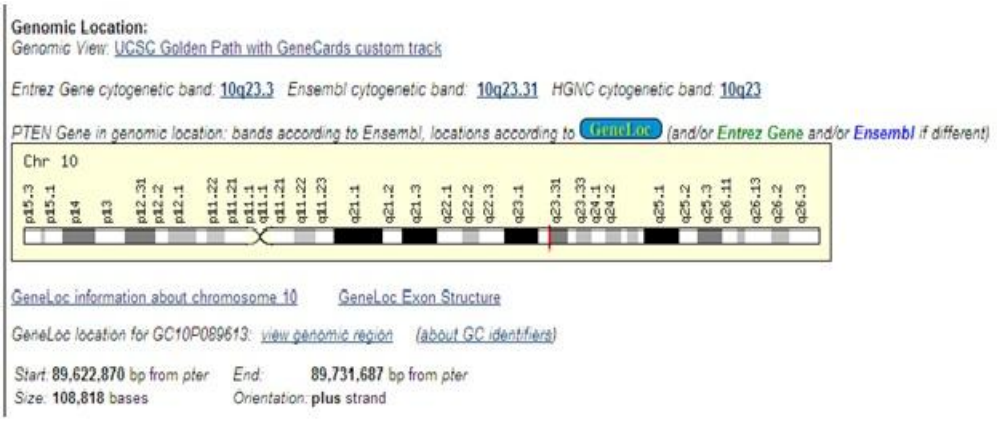


Figure3: a and b showing GeneCard result

Via GeneCard the information about the PTEN gene is found. And the genomic location is found on the chromosome 10 which has the size of 108.818 bases. It also showed the various pathways related to the PTEN. ProtParam tool provides us with the physiochemical properties of query entered, like: the query sequence has 403 a.a with molecular weight of 47166.2; the isoelectric point comes as 5.22. It has max. Lysine residues 8.4% negatively charged residues are more than positively but the difference is minor. Total no. of atoms being 6538.The estimated half-life is: 30 hours. The instability index (II) is computed to be 44.21, aliphatic index: 66.97, more this index more will be the extended structure of the protein.

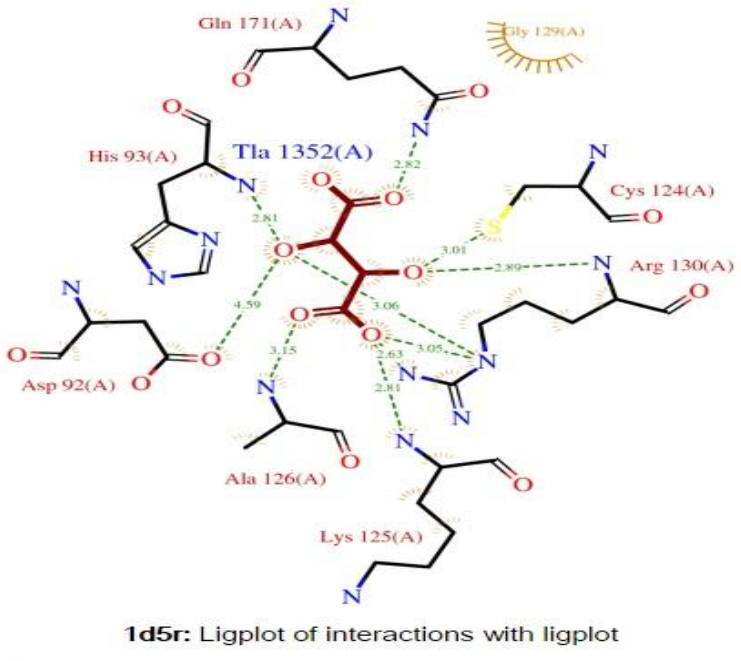
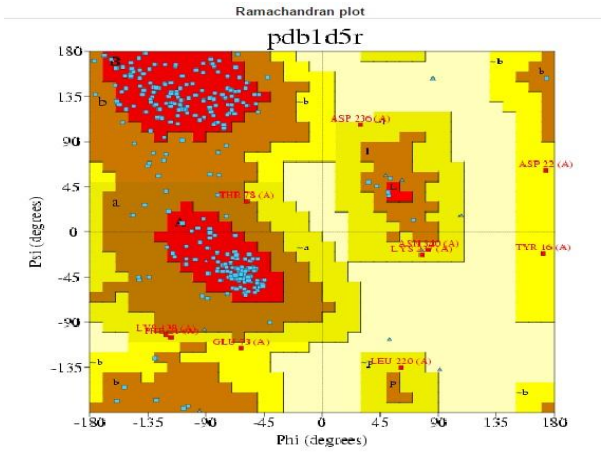
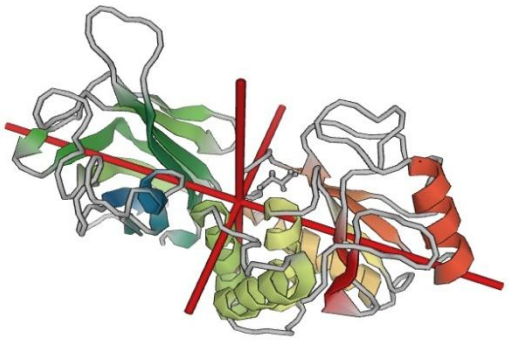


Figure4: Ligand Tla 1352 showing in this structure

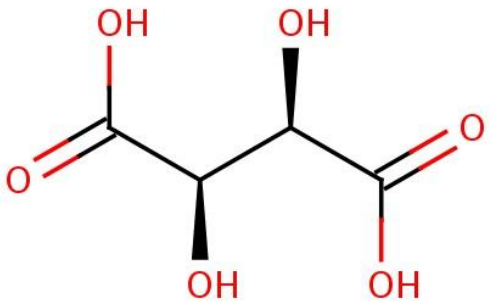


(A)



(B)

(C)



(D)

Figure5: (a) Ramachandran Plot, (b) & (c) Ligand in tertiary structure form, (d) Ligand in secondary structure form.

The following is the graphical representation of the HSP found by BLAST. Please note that HSPs are sorted from highest to lowest scores, so that lower scoring HSPs may be hidden. In this I found 13 domains of the protein out of which I chose the highest length of 360 a.a with the score of 147 >PD991576 (Closest domain: Q6CCA7_YARLI 121-480).

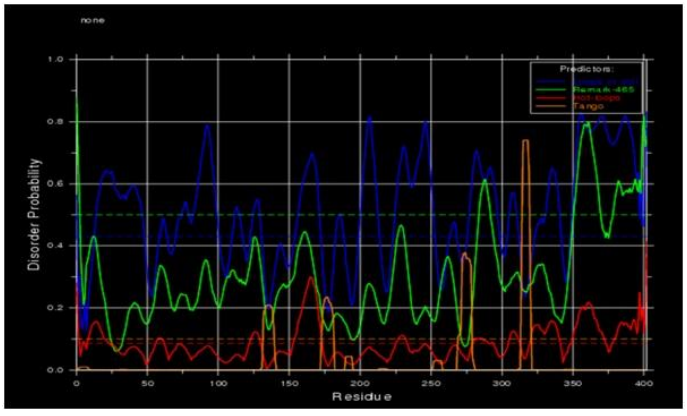


Figure6: It showing disorder probability region.

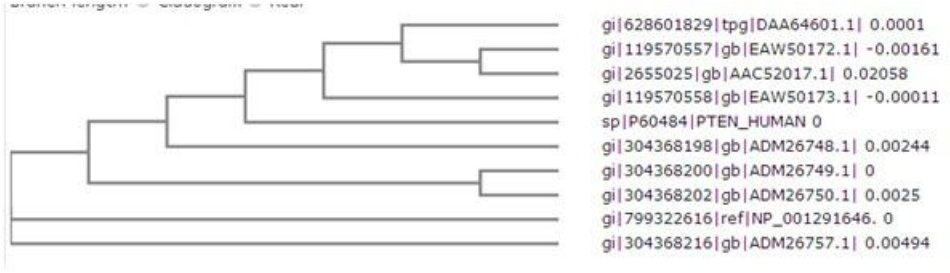


Figure7: It showing evolutionary relationship

#	Template	Alignment Coverage	3D Model	Confidence	% i.d.	Template Information
1	c1d5rA	Alignment		100.0	99	**PDB header:**hydrolase **Chain:** A: **PDB Molecule:**phosphoinositide phosphotase pten; **PDBTitle:** crystal structure of the pten tumor suppressor
2	c3awfC	Alignment		100.0	37	**PDB header:**hydrolase, membrane protein **Chain:** C: **PDB Molecule:**voltage-sensor containing phosphatase; **PDBTitle:** crystal structure of pten-like domain of ci-vsp (236-576)
3	c3n0aA	Alignment		100.0	28	**PDB header:**hydrolase **Chain:** A: **PDB Molecule:**tyrosine-protein phosphatase auxilin; **PDBTitle:** crystal structure of auxilin (40-400)
4	d1d5ra2	Alignment		100.0	100	**Fold:**(Phosphotyrosine protein) phosphatases II **Superfamily:**[Phosphotyrosine protein) phosphatases II **Family:**Dual specificity phosphatase-like

Figure8: It showing template for target gene.

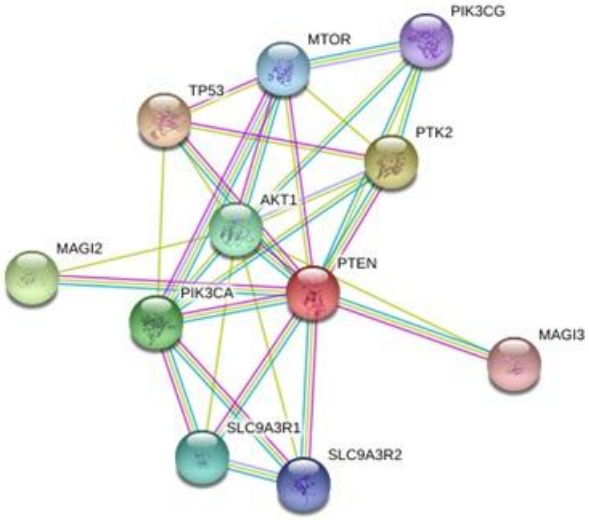


Figure9: Interrelation network between different genes and proteins with PTEN and AKT1.

PROSITE offers tools for protein sequence analysis and motif detection. Here Prosite tells the PTEN protein of 403 bases has a motif from 122-132. Fingerprint scan results gave 10 motifs out of which I chose the one with highest score 500(NUR). According to disEMBL highest disorders in the loop and coil regions have been found in between 350-403 residues.in the hot loops region highest disorder is between 379-403 residues and in the remark—465 definition maximum disorder is between 379-403 residues**.**

CONCLUSION

Proteus syndrome is a rare disorder. It consists asymmetric and disproportionate overgrowth in bones and skins. AKT1 and PTEN genes are responsible for proteus syndrome. In the present work, I have analyzed the results of PTEN gene which is responsible for proteus syndrome. It has 2.1 Å resolutions which is the best resolution for further analysis. So, I took PTEN gene for further analysis. It consists 403 aa in the length. It homology modeling of this is an important step towards the drug designing process. The modeling can be used for the further advancement or the further research. The ligand TLA(1352) is found and the process can lead to the further discovery of the drug for the proteus syndrome

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