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HOMOLOGY MODELLING AND SIMULATION STUDY OF PARKIN PROTEIN FROM HOMOSAPIENS AT 310K

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ABSTRACT

Parkinson's disease (PD) is a slowly progressive disorder that affects movement, muscle control, and balance. It is characterized by the loss of dopaminergic neurons in the substantia nigra and accumulation of Lewy bodies. An early onset form of Parkinson's disease (AR-JP) has been associated with a loss of function mutation in the gene parkin, although in this form Lewy bodies do not accumulate. Mutations in Parkin are a major cause of autosomal recessive juvenile Parkinsonism. Parkin lacks exon 4 which encodes amino acid residues 179 - 206 of Parkin. Tertiary Structure of Parkin protein has not yet been solved. So in our present work we will model the structure of Parkin using Modeller9v1 and Validate the modeled structure by RMSD Calculation using Combinatorial Extension and by plotting the Ramachandran graph using Procheck. Then the modeled structure will be subjected to Molecular Dynamics Studies using GROMACS.

1.INTRODUCTION

Parkinson's disease (PD) is a slowly progressive disorder that affects movement, muscle control, and balance. Parkinson's disease is referred to as idiopathic, which means that the cause is unknown. This term distinguishes the primary disease from parkinsonism , which are the symptoms occurring from a known cause.[1-5] In addition to its effects on motor control, Parkinson's disease is now recognized as a broader condition that can include cognitive and behavioral disturbances, sleep disorders, speech difficulties, and other problems.
Parkinson's Disease and Dopamine Loss

Parkinson's disease occurs from the following process in the brain:

- PD develops as cells are destroyed in certain parts of the brain stem, particularly the crescent-shaped cell mass known as the substantia nigra .

Parkinson's disease is a slowly progressive disorder that affects movement, muscle control, and balance. Part of the disease process develops as cells are destroyed in certain parts of the brain stem, particularly the crescent-shaped cell mass known as the substantia nigra. Nerve cells in the substantia nigra send out fibers to tissue located in both sides of the brain. There the cells release essential neurotransmitters that help control movement and coordination.

- Nerve cells in the substantia nigra send out fibers to the corpus stratia , gray and white bands of tissue located in both sides of the brain.
- There the cells release dopamine , an essential neurotransmitter (a chemical messenger in the brain). Loss of dopamine in the corpus stratia is the primary defect in Parkinson's disease. [6-11]

Dopamine. Dopamine deficiency is the hallmark feature in PD. It is one of three major neurotransmitters known as catecholamines , which help the body respond to stress and prepare it for the fight-or-flight response. Loss of dopamine negatively affects the nerves and muscles controlling movement and coordination, resulting in the major symptoms characteristic of Parkinson's disease. Dopamine also appears to be important for efficient information processing, and deficiencies may also be responsible for problems in memory and concentration that occur in many patients.

Although it is clear that dopamine deficiency is the primary defect in Parkinson's disease, it is not clear what causes dopamine loss. The culprit is less likely to be a single cause than a combination of genetic and biologic factors, which are triggered by some environmental assault.[12-19]

4.MATERIALS AND METHODS

4.1. MATERIALS:

This section describes the tools and databases used in due course of the project work.

4.2. DESCRIPTION OF DATABASES USED:

NCBI

Website: www.ncbi.nlm.nih.gov

Biology today is being transformed by an explosive growth of data emerging from laboratories worldwide. [20-25]The challenge is to transform data into knowledge, knowledge that will lead to a better understanding of the biological processes underlying both health and disease. The quest for this knowledge drives NCBI investigators to develop new methods for integrative, computer-based data analysis to mine massive and complex datasets.

4.3. DESCRIPTION OF TOOLS USED:

Basic Local Alignment Search Tool (BLAST)

Website: www.ncbi.nlm.nih.gov/blast

The discovery of sequence homology to a known protein or family of proteins often provides the first clues about the function of a newly sequenced gene. As the DNA and amino acid sequence databases continue to grow in size they become increasingly useful in the analysis of newly sequenced genes and proteins because of the greater chance of finding such homologies.

4.4. METHODS

4.4.1. STEPS IN HOMOLOGY MODELING

1. Identify a template protein for the target sequence (Sequence of the protein for which the structure is not present in Protein Data Bank.
1. Domain search was done using Pfam.
2. Alignment between the target and template sequence was done by using the malign.py program of Modeller9v1 package.
3. Tertiary structure of the target sequence is modeled using the model-default.py program of Modeller9v1 package.
4. Modelled Structure was validated by

   4.1 Calculating the Root Mean Square Deviation (RMSD) value between the target and the template. RMSD calculation between the target and template will help us identify the deviation between the target structure and the template structure.

   4.2 Plotting the Ramachandran Plot.

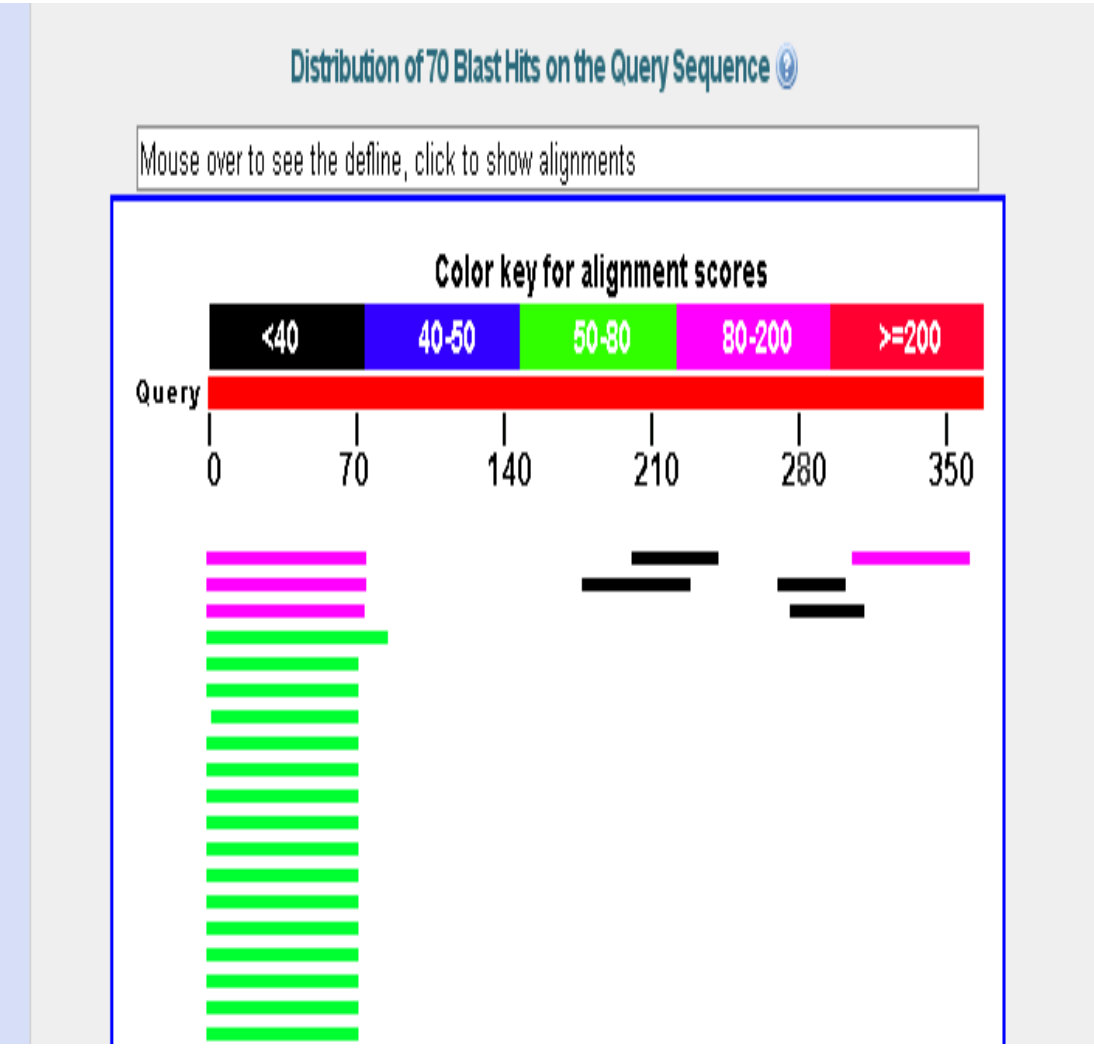
5.RESULTS & DISCUSSION

TARGET PROTEIN ID

```
FEATURES             Location/Qualifiers
     source          1..368
                     /organism="Homo sapiens"
                     /db_xref="taxon:9606"
                     /chromosome="6"
                     /map="q25.3-27"
                     /clone="RP1-45F6"
                     /clone_lib="RPCI-1"
     Protein         1..368
                     /product="Parkinson disease (autosomal recessive,
                     juvenile) 2, parkin"
     Region          3..72
                     /region_name="parkin_N"
                     /note="parkin_N  parkin protein is a RING-type E3
                     ubiquitin ligase with an amino-terminal ubiquitin-like
                     (Ubl) domain and an RBR signature consisting of two RING
                     finger domains separated by an IBR/DRIL domain.  Naturally
                     occurring mutations in parkin are...; cd01798"
                     /db_xref="CDD:29200"
     Site            42
                     /site_type="other"
                     /note="Arg42Pro mutation site"
                     /db_xref="CDD:29200"
     CDS             1..368
                     /gene="PARK2"
                     /locus_tag="KB-152G3.1-002"
                     /standard_name="OTTHUMP00000017563"

ORIGIN
        1 mivfvrfnss hgfpvevdsd tsifqlkevv akrqgvpadq lrvifagkel rndwtvqncd
       61 ldqqsivhiv qrpwrkgqem natggddprn aaggcerepq sltrvdlsss vlpgdsvgla
      121 vilhtdsrkd sppagspagr siynsfyvyc kgpcqrvqpg klrvqcstcr qatltltqgp
      181 scwddvlipn rmsgecqsph cpgtsaefff kcgahptsdk etsvalhlia tnsrnitcit
      241 ctdvrspvlv fqcnsrhvic ldcfhlycvt rlndrqfvhd pqlgyslpcv agcpnslike
      301 lhhfrilgee qynryqqyga eecvlqmggv lcprpgcgag llpepdqrkv tceggnglgc
      361 gygqrrtk
//
```

TARGET PROTEIN INFORMATION



5.1. SIMILARITY ANALYSIS- BLAST RESULT

5.2. C-MODELLER FILES:

```
Modeller
You can find many useful example scripts in the
examples\automodel directory.
Type 'mod9v1' to run Modeller.

C:\Program Files\Modeller9v1>E:

E:\>cd manu

E:\manu>mod9v1 malign.py
'import site' failed; use -v for traceback

E:\manu>mod9v1 model-default.py
'import site' failed; use -v for traceback
```

Modeller9v1

Fig.1. MODELED STRUCTURE OF PARKIN

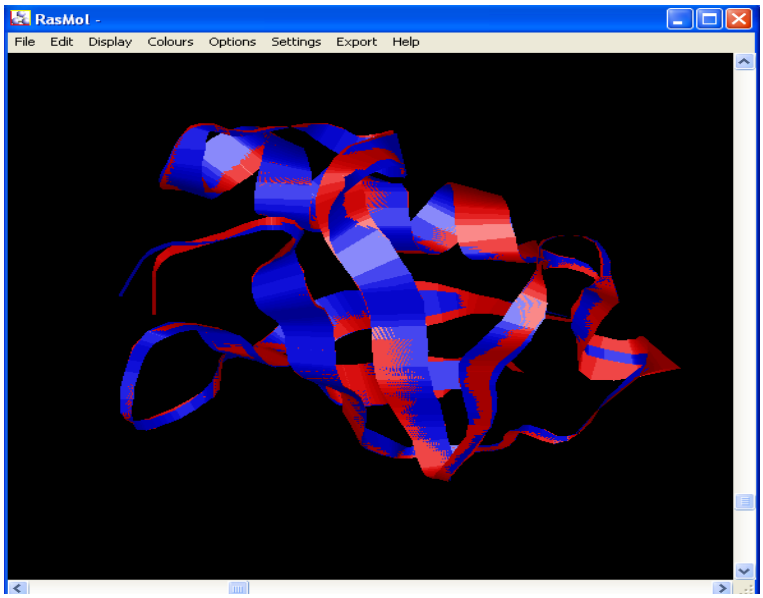
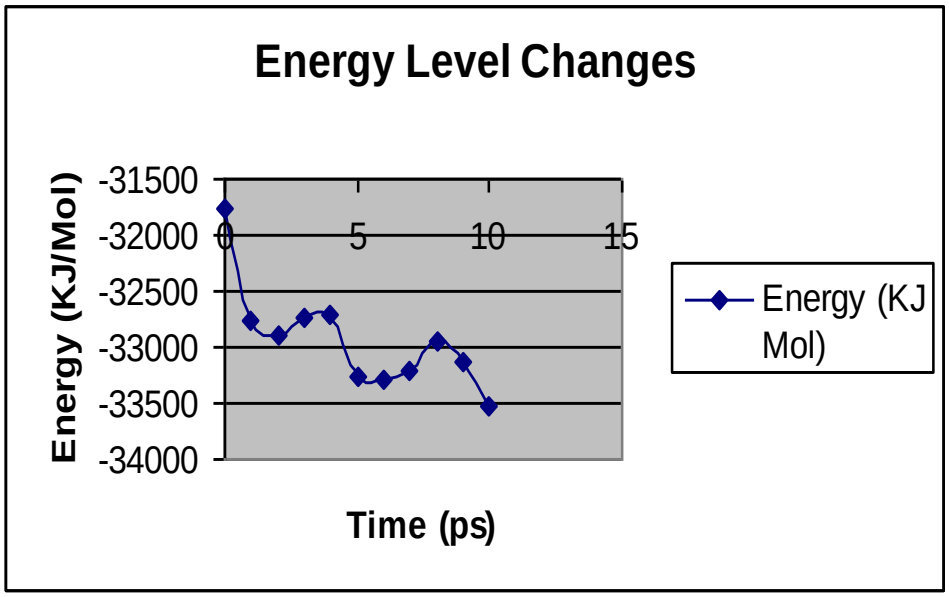


Fig.2. SUPERIMPOSED STRUCTURE

G ENERGY – ENERGY CALCULATION

Time (.ps)	Energy (KJ Mol)
0	-31760.74564
1	-32756.64619
2	-32894.6459
3	-32749.19219
4	-32712.68521
5	-33263.14878
6	-33285.78755
7	-33198.75356
8	-32957.94619
9	-33133.02631
10	-33526.49231

ENERGY VALUES



5.5. ENERGY GRAPH

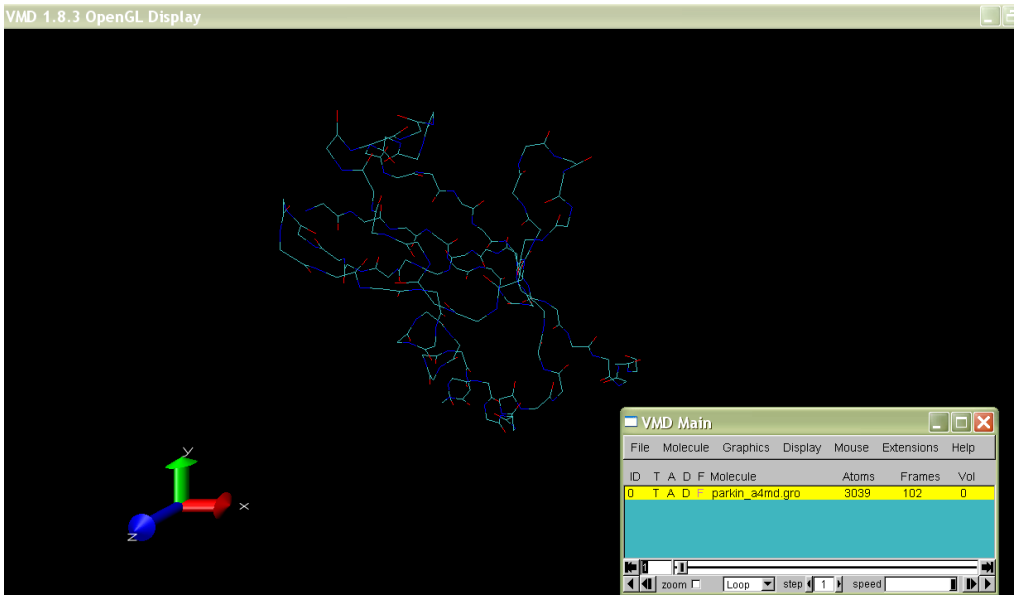


Fig.5. MOLECULE VISUALIZED AT 1 PICO SEC

5.6. DISCUSSION

The protein sequence of *parkin* sequence was obtained from GenBank. Domain analysis against Pfam database suggests the presence of a ubiquitin family sequence from 8 to 76. Modeling template was searched by using PBLAST. BLAST suggests 2ZEQ (PDB ID) as a template with a identity of 89%. Molecular structure of Parkin from *Homo sapiens* was modeled by using MODELLER 9v1. Molecular Dynamics Simulation was performed with GROMACS to obtain the structural information of parkin at 310.15 K (37°C) in aqueous environment. Parkin was simulated with the OPLS all-atom force field with the GROMACS molecular dynamics package. Energy minimization was performed to remove the overlapping atoms. Simulated structure was used to study the energy level changes. The values were recorded and graph was plotted.[26-45]

6. CONCLUSION

Parkin is the protein which may be the cause of Parkinson's disease (PD) in humans.The protein is involved in ubiquitin-proteasome system for the clearance of misfolded proteins and other target molecules. It also serves as the E3 enzyme in the system.Parkin codes for parkin 2 gene and the mutations caused in this gene causes the parkinsons disease .the structutre is modeled for parkin and validation of the modeled structure suggests that the modeled structure is a good model. Molecular Dynamics Simulation study of parkin suggest that the energy is getting minimized from initial structure to the simulated structure. The simulated structure is visualized and the changes in the protein structure at different picoseconds are noted .Further molecular dynamics study of the parkin protein at different temperature will help us in understanding its influence in parkinsons disease.

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