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Structure Prediction of Delta Aminolevulinic Acid Dehydratase (ALAD); An Enzyme that is Very Sensitive to the Toxic Effects of Lead

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Abstract

The ALAD (Aminolevulinic Acid Dehydratase) gene polymorphism is linked with the accumulation of lead in the bone, blood and the other internal organs and it may predispose for many critical symptoms in the lead exposed persons. The aim of this study is to determine the primary, secondary and tertiary structure of lead. This enzyme is susceptible towards the toxic effect of lead. Primary structure prediction was done by Protparam tool, Compute PI/MW tool, Proscale tool. Secondary structure prediction was done by Self –optimize prediction method (SOPMA) tool, Porter tool. Tertiary structure prediction was done by protein structure prediction server. Domain was determined by Simple Modular Architecture Research (SMART) tool.

Keywords: ALAD; Toxic effects; Lead

Introduction

Lead is an environmental toxic metal, which is capable of causing many chronic diseases. Important sources of lead include pipes, lead containing paints, gasoline containing lead, and the different kinds of canned foods. Lead is distributed in the bone, blood and the soft tissues after absorption. There is about 99% lead bounds to the red blood cells, and 1% is present in the plasma, and it is available for the exchange in other tissues. There is 30 days half-life of lead in persons having a normal renal function but it becomes longer in those who have the renal insufficiency [1].

Oxidative stress is a very major effect of lead [2]. The mechanism of lead-induced oxidative stress involves an imbalance between generation and removal of ROS (Reactive Oxygen Species) in tissues and cellular components causing damage to membranes, DNA and proteins [3]. Oxidative stress causes oxidation of membrane lipoproteins and oxidation of DNA leading to tissue damage.

The ALAD (aminolevulinic acid dehydratase) gene polymorphism is linked with the accumulation of lead in the bone, blood and the other internal organs and it may predispose for many critical symptoms in the lead exposed persons. There are a lot of different reports here that give us information about the neurotoxic effects of the lead on the workers exposed to lead [4].

Methodology

The sequence of Delta aminolevulinic acid dehydratase (ALAD) was taken from National center for Biotechnology Information (NCBI). Accession number of sequence that was studied in this project is AAC60582.1. The structure of this sequence was predicted by several tools. Bioinformatics tools were used for determination of primary, secondary and tertiary structure of amino levulinic acid dehydratase (ALAD). Primary structure prediction was done by Protparam tool, Compute PI/MW tool, Proscale tool. Secondary structure prediction was done Self –optimize prediction method (SOPMA) tool, Porter tool. Tertiary structure prediction was done by protein structure prediction server. Domain was determined by Simple Modular Architecture Research (SMART) tool.

Results

According to proparam tool its Amino acid sequence is 330, Molecular weight is 36324.9 Dalton and Theoretical PI value is 6.32, formula is $C_{1619}H_{2549}N_{4470465}S_{19}$.

Total numbers of atoms are 5099, Extinction coefficient is 34880, Estimated half-life is 30 hours, Instability index is 46.43, Aliphatic index is 89.33. Grand average of hydropathicity is -0.043, Total number of negatively charged residues (Asp + Glu) are 38 and Total number of positively charged residues (Arg + Lys) are 35. Its amino acid composition is given below:

Amino acid composition

The amino acid composition was given in Table 1.

Atomic composition

The atomic composition was explained in Table 2 and Figure 1.

According to porter tool

MQPQSVLHSGYFHPLLRAWQTATTTLNASNLIYPIFVTDVP-DDIQPITSLPGVARYGVKR

CCCCCCCCHHHCCCHHHHHHHHHCCCCCCCHH-HEEEEEEEECCCCCEEECCCCCCCEEECHHH

Atomic composition		
Carbon	C	1619
Hydrogen	H	2549
Nitrogen	N	447
Oxygen	O	465
Sulfur	S	19

Table 1: Amino acid composition.

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Amino acid composition		
Ala (A)	39	11.8%
Arg (R)	23	7.0%
Asn (N)	5	1.5%
Asp (D)	18	5.5%
Cys (C)	8	2.4%
Gln (Q)	10	3.0%
Glu (E)	20	6.1%
Gly (G)	23	7.0%
His (H)	9	2.7%
Ile (I)	12	3.6%
Leu (L)	35	10.6%
Lys (K)	12	3.6%
Met (M)	11	3.3%
Phe (F)	12	3.6%

Source: According to Compute PI/Mw its Theoretical pI/Mw is 6.32/36324.91 Dalton

Table 2: Tables Shows the Atomic composition.

Name	Begin	End	E-Value
ALAD 2	327	9.53	e-181

Table 3: Confidently predicted domains, repeats, motifs and features.

Name	Begin	End	E-Value	Reason
YccV-LIKE	53	151	1.53E+05	Threshold
DWA	53	139	3.9e+03	Threshold
MR-MLE	61	181	1.59e+05	Threshold
PHD	109	163	1.78.+03	Threshold
PTI	110	133	3.47+02	Threshold
CGCG	116	196	3.61e+04	Threshold
IB	117	176	1.44e+03	Threshold
ChtBD1	121	144	1.26e+03	Threshold
CM-2	142	204	1.41e+05	Threshold
HTH-ARAC	144	222	2.26e+03	Threshold
SAP	170	201	1.65e+05	Threshold
HMG	252	309	2.62e+03	Threshold

Table 4: These features and domains are not shown in the diagram, either because their scores are less significant than the required threshold, or because they overlap some other source of annotation.

LEEMLRPLVEEGLRCVLIFGVPSRVPKDERGSAADSEESPAIEAIHLLRKTFPNLLVACD

HHHHHHHHHHCCCCEEEEEEECCCCCCCCCCHHHHCCCCHHHHHHHHHHHHCCCCEEEEE

VCLCPYTSHGHCGLLSENGAFRAEESRQRLAEVALAYAKAGCQVVAPSDMMDGRVEAIKE

ECCCCCCCCCCCCCECCCCCECCHHHHHHHHHHHHHHHHHHHCCCEEEECCCCCCHHHHHHH

A L M A H G L G N R V S V M S Y S A K F A S C F Y G P F R D A A K S S P A F G D R R C Y Q L P P G A R G L A L R A V D R H H H H C C C C C C C E E E E E E E E E C C C C C H H H H H H H HCCCCCCCCCCCCCECCCCHHHHHHHHHHH

DVREGADMLMVKPGMPYLDIVREVKDKHPDLPLTVYHVSGEFAMLWHGAQAGAFDLKAAV

H H H C C C C E E E E E C C H H H H H H H H H H H H H HCCCCCEEEEECHHHHHHHHHHHHCCCCCHHHHH

LEAMTAFRRAGADIIITYYTPQLLQWLKEE

HHHHHHHHHHCCCEEEECCHHHHHHHCCCC

(seq. similarity up to 98.5%).

According to SOPMA

Alpha helix (Hh) : 141 is 42.73%, 3_{10} helix (Gg) : 0 is 0.00%, Pi helix (Ii) : 0 is 0.00%, Beta bridge (Bb) : 0 is 0.00%, Extended strand (Ee) : 52 is 15.76%, Beta turn (Tt) : 30 is 9.09%, Bend region (Ss) : 0 is 0.00%, Random coil (Cc) : 107 is 32.42%, Ambigous states (?) : 0 is 0.00%, Other states: 0 is 0.00% (Figure 2) (Tables 3 and 4).

Discussion and Conclusion

Lead is recognized as a toxic metal that is the cause of many dangerous diseases in humans. It is considered as the most clinically important heavy metal because it induces a broad range of physiological, biochemical, and behavioral dysfunctions. One of the major mechanisms by which lead exerts its toxic effect is through biochemical processes that include lead's ability to inhibit or mimic the actions of calcium and to interact with proteins. Many investigators have demonstrated that lead intoxication induced cellular damage mediated by the formation of reactive oxygen species [5].

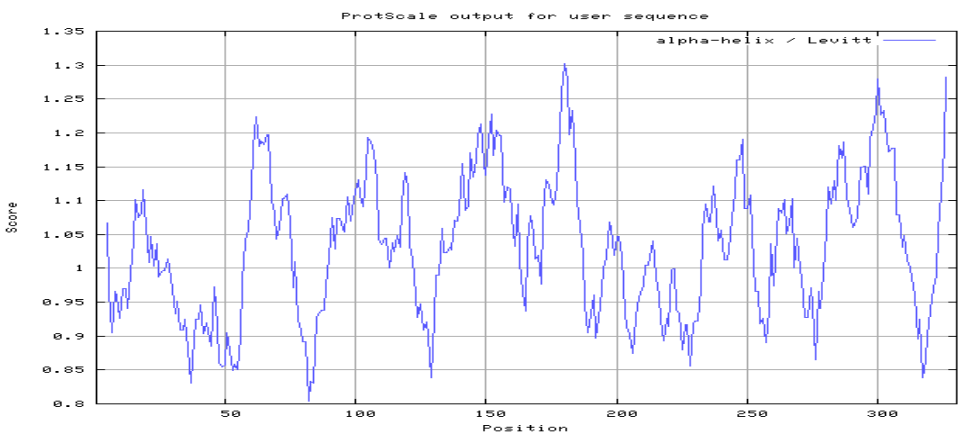
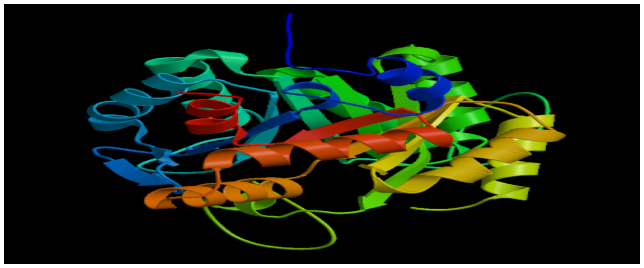


Figure 1: Below represents the Graphical form of ProtsScale.



Domain of ALAD

Figure 2: Shows the Tertiary structure of ALAD.

According to primary structure prediction tools the molecular weight of Aminolevulinic acid dehydratase (ALAD) is 36324.9 Dalton, Theoretical Isoelectric Point value is 6.32 and number of amino acids are 330 which is supported by previous studies. It was proposed by Farant and Wigfield [6] Aminolevulinic acid dehydratase is highly sensitive to the toxic effects of lead.

Protein structure prediction server was developed by Chen [7] for determination of tertiary structure of proteins. In this study tertiary structure of aminolevulinic acid dehydratase is determined by protein structure prediction server that used PSI-BLAST and IMPALA for template selection, T-Coffee for target-template alignment, MODELLER for model building and CHIME for visualization of protein model.

SMART (simple modular architecture research tool) tool was developed by Schultz [8] that allows rapid identification of signaling domains of proteins and annotation of signaling domain sequences of proteins. The tool contains several unique aspects, including automatic seed alignment generation, automatic detection of repeated motifs or domains, and a protocol for combining domain predictions from homologous subfamilies. In this study domain of Aminolevulinc acid dehydratase is determined by the use of SMART tool. This tool predicts one domain of Aminolevulinic acid dehydratase [9].

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