ANALYSIS OF PHENYLKETONURIA (PKU) BY USING INTERPROSCAN
S. R. Deshmukh, Bushra J. Pathan, S. S. Bhalke, P. S. Deshmukh, Choubey S.*
MGM college of CS and IT Nanded 431605
*Yeshwant college of IT, Bioinformatics and Biotechnology, Parbhani

Abstract:
Phenylalanine hydroxylase (PAH) is the enzyme that converts phenylalanine to tyrosine as a rate-limiting step in phenylalanine catabolism and protein and neurotransmitter biosynthesis. Deficient enzyme activity leads to the disorders like hyperphenylalaninaemia and phenylketonuria. The determination of the crystal structure of PAH now allows the determination of the structural basis of mutations resulting in PAH deficiency.
We present an analysis of the structural basis of 120 mutations with a 'classified' biochemical phenotype and/or available in vitro expression data. We have found that the mutations can be grouped into five structural categories, based on the distinct expected structural and functional effects of the mutations in each category.
Structural information helps to formulate some rules that will help to predict the likely effects of unclassified and newly discovered mutations: proteins with truncations and large deletions, fusion proteins and active site mutations generally cause severe phenotypes; domain structure mutations and dimer interface mutations spread over a range of phenotypes.

Keywords: phenylalanine hydroxylase, biochemical phenotype, mutations hyperphenylalaninaemia, phenylketonuria.

INTRODUCTION:
Phenylketonuria (PKU) is an autosomal recessive genetic disorder characterized by a deficiency in the hepatic enzyme phenylalanine hydroxylase (PAH). Phenylalanine hydroxylase is a tetramer composed of four monomers, that is, composed of 4 identical subunits. Each subunit is in turn composed of three domains, a regulatory domain, a catalytic domain, and a tetramerization domain.

PKU is normally detected using the HPLC test, but some clinics still use the Guthrie test, part of national biochemical screening programs. Most babies in developed countries are screened for PKU soon after birth.

Structures
Phenylalanine hydroxylase is a tetramer composed of four monomers, that is, composed of 4 identical subunits. Each subunit is in turn composed of three domains, a regulatory domain, a catalytic domain, and a tetramerization domain.

The regulatory domain is composed of the approximately 115 amino acids
nearest the amino terminal of the subunit.

The catalytic domain is composed of the next approximately 300 amino acids, and is responsible for all of the catalytic activity of the enzyme.

The tetramerization domain consists of the remaining amino acids and through the formation of a coiled-coil arrangement of amino acids, holds the tetrameric structure of the holoenzyme together with a leucine zipper. Phenylalanine hydroxylase contains one bound iron atom per subunit which is necessary for catalytic activity.

Fig 1: Normal Metabolism of phenylalanine

There are two routes by which the excess Phe can be metabolized: oxidation to tyrosine (the normal and main route for degradation of Phe, and the normal route for biosynthesis of phenylpyruvate and subsequent further metabolism (a minor route, which comes to the fore when the main route is blocked).

Fig 2: Abnormal Metabolism of Phenylalanine

Consequences of a Block in the
Oxidation of Phenylalanine

When the main route of degradation of Phe is blocked, then serum concentrations of Phe and its metabolites will rise. Three forms of hyperphenylalaninemia (HPA) can be distinguished, based on serum concentrations of phenylalanine: benign, variant, and classic.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Normal</th>
<th>Benign HPA</th>
<th>Variant HPA</th>
<th>Classic HPA / Classic PKU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylalanine</td>
<td>approx. 1 mg/dL (0.061 mM)</td>
<td>4-10 mg/dL (0.242-0.605 mM)</td>
<td>10-20 mg/dL (0.605-1.21 mM)</td>
<td>above 20 mg/dL (above 1.21 mM)</td>
</tr>
</tbody>
</table>

Under conditions of hyperphenylalaninemia a minor route of Phe metabolism becomes important. The minor route for degradation of Phe starts with the transamination of Phe to phenylpyruvate:

**Fig3: Transamination of Phenylalanine to Phenylpyruvate**

This transamination reaction is a standard one in the metabolism of amino acids. Note the role of alpha-ketoglutarate as the acceptor of the amino group from Phe, with consequent formation of glutamate.

The phenylpyruvate is further metabolized. Decarboxylation of phenylpyruvate gives phenylacetate, while a reduction reaction gives phenyl lactate. The phenylacetate can be further conjugated with glutamine to give phenylacetyl glutamine. All of these metabolites can be detected in serum and urine by suitable clinical tests.

**Materials and Methods:**

1) NCBI-ENTREZ

**CROSSDATABASE SEARCH**

When it comes to getting information on sequences and databases, many paths lead to the National Center for Biotechnology Information (NCBI). The ENTREZ databases and querying system developed at NCBI offers a powerful and relatively simple way to search most of NCBI’s numerous databases. The main drawback with ENTREZ was that only one database could be accessed at a time.

**mRna Sequence of PAH [NM_000277]**

**Fig: 4 Results: Interproscan**
ACKNOWLEDGEMENT:-
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CONCLUSION:
A Deficiency in PAH activity cause PKU. This PKU can be detected through Patients urine and serum. A person suffering from this disease they have to face many problems like mental retardation and seizures. However, PKU is one of the few genetic diseases that can be controlled by diet. A diet low in phenylalanine and high in tyrosine can be a very effective treatment. There is no cure. Damage done is irreversible so early detection is crucial.

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