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ANALYSIS OF PHENYLKETONURIA (PKU) BY USING INTERPROSCAN

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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 find 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). [1] This enzyme is necessary to metabolize the amino acid phenylalanine ('Phe') to the amino acid tyrosine. When PAH is deficient, phenylalanine accumulates and is converted into phenylpyruvate (also known as phenylketone), which is detected in the urine.[2]

Phenylketonuria was discovered by the Norwegian physician Ivar Asbjørn Folling in 1934[3] when he noticed that hyperphenylalaninemia (HPA) was associated with mental retardation. In Norway, this disorder is known as Falling's disease, named after its discoverer.[4]

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. [5]

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.

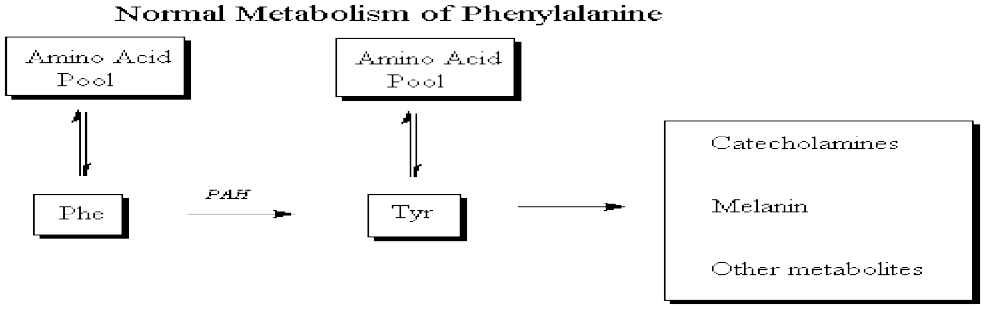
The *tetramerization domain* consists of the remaining amino acids and through the formation of a coiled-coil arrangement of amino acids, holds the tetrameric structure of the holoenzyme together with a leucine zipper.
Phenylalanine hydroxylase contains one bound iron atom per subunit which is necessary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

Normal catabolism of phenylalanine

In humans, phenylalanine is normally oxidized by the enzyme phenylalanine hydroxylase (*PAH*) to form the amino acid tyrosine; this is in fact the normal biosynthetic route to tyrosine for humans. From tyrosine, there are further connections to the biosynthesis of catecholamines, melanin, hormones, etc. Usually, dietary intake of Phe and Tyr, and the body's demand for Phe and Tyr, are fairly closely balanced. However, when there is too much phenylalanine in the body's pool of amino acids, it must be eliminated, either by excretion or by biochemical reaction.

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 Tyr), and transamination to phenylpyruvate and subsequent further metabolism (a minor route, which comes to the fore when the main route is blocked).



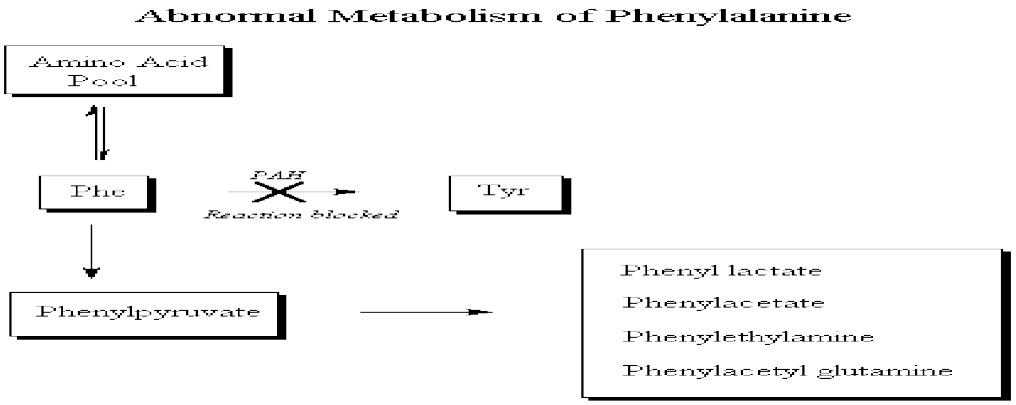


Fig 2: Abnormal Metabolism of Phenylanine

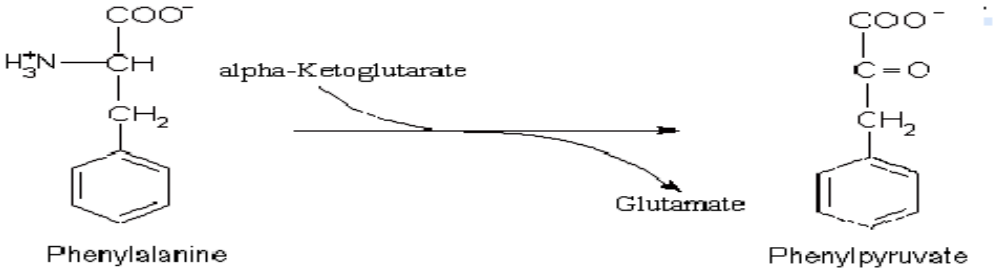
Consequences of a Block in the

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 1:

Compound Concentration	Normal	*Benign* HPA	*Variant* HPA	*Classic* HPA / Classic PKU
Phenylalanine	approx. 1 mg/dL (0.061 mM)	4-10 mg/dL (0.242-0.605 mM)	10-20 mg/dL (0.605-1.21 mM)	above 20 mg/dL (above 1.21 mM)



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.

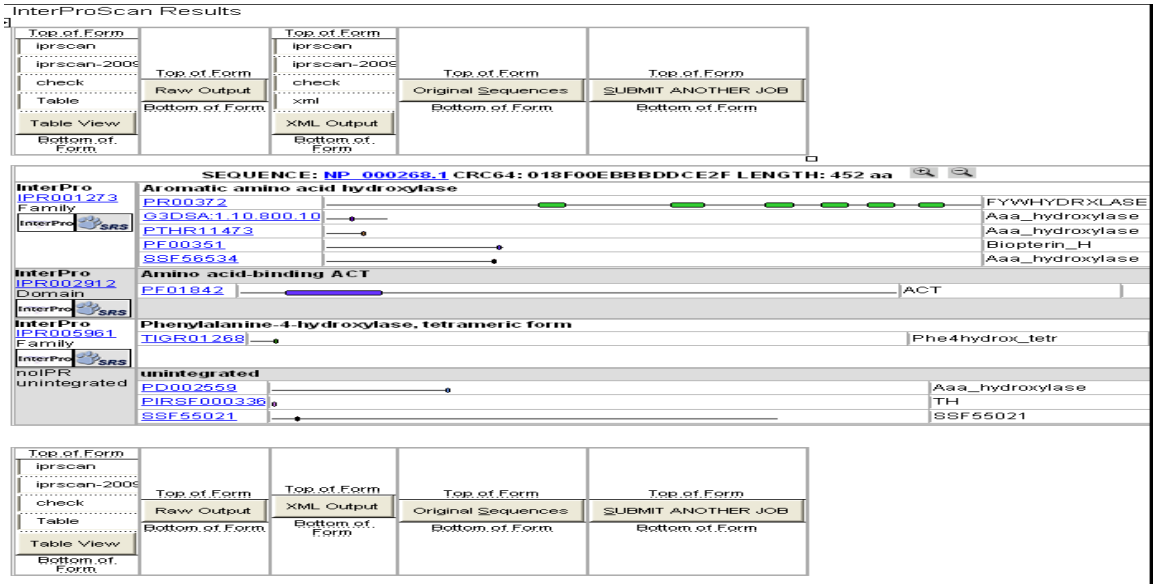
Materials and Methods:

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



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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 treat ment. There is no cure. Damage done is irreversible so early detection is crucial.

REFERENCES:

1. James, William D.; Berger, Timothy G.; et al. (2006). *Andrews' Diseases of the Skin: clinical Dermatology*. Saunders Elsevier. ISBN 0-7216-2921-0.
2. cite journal - author=Gonzalez, Jason; Willis, Monte S. - date=Feb. 2010 - title=Ivar Asbjorn Folling Discovered Phenylketonuria (PKU) - journal=lab medicine - volume=41 - number=2 - pages=118-119
3. Folling, A. (1934). "Ueber Ausscheidung von Phenylbrenztraubensaeure in den Harn als Stoffwechselanomalie in Verbindung mit Imbezillitaet". *Ztschr. Physiol. Chem.* 227: 169–176.
4. Centerwall, S. A. & Centerwall, W. R. (2000). "The discovery of phenylketonuria: the story of a young couple, two affected children, and a scientist.". *Pediatrics* 105 (1 Pt 1): 89–103. doi: 10.1542/peds.105.1.89. PMID 10617710. http://pediatrics.aappublications.org/cgi/content/full/105/1/89.
5. Mayo Clinic Staff (2007-12-20). "Phenylketonuria (PKU)". Mayo Clinic. http://www.mayoclinic.com/health/phenylketonuria/DS00514/DSECTION=1. Retrieved 2008-03-13.

Web References

1) www.ncbi.nlm.nih.gov.com
2) www.ebi.ac.uk/Tools/InterProScan