P-3098

BIOLOGICAL DATABASE CREATION OF PROTEIN METABOLIC DISORDERS

(Amino acid deficiency disorder database (A^2D^2DB))

PROJECT REPORT

Submitted by

M.D.VAISHNAVA MURARI

Register No: 0820203015

in partial fulfillment for the award of the degree

Of

MASTER OF TECHNOLOGY

in

BIOTECHNOLOGY

KUMARAGURU COLLEGE OF TECHNOLOGY, COIMBATORE-06.

(An Autonomous Institution affiliated to Anna University, Coimbatore)

MAY 2010

Certificates

ANNA UNIVERSITY:COIMBATORE

BONAFIDE CERTIFICATE

KUMARAGURU COLLEGE OF TECHNOLOGY

COIMBATORE-641 006

Department of Biotechnology

PROJECT WORK -PHASE II

MAY 2010

This is to certify that the project entitled **BIOLOGICAL DATABASE CREATION OF PROTEIN METABOLIC DISORDERS** is the bonafide record of project work done by **M.D.VAISHNAVA MURARI Register No: 0820203015** of M.Tech during the year 2009-2010.

Dr. P.RAMALINGAM

Assistant Professor

Department of Biotechnology

Kumaraguru College of Technology

Coimbatore - 641 006

Dr. S.SADASIVAM

Dean - Biotechnology

Department of Biotechnology

Kumaraguru College of Technology

Coimbatore - 641 006

Submitted for the Project Viva-Voce examination held on 17th May '10.

Internal Examiner

External Examiner 19.5.10

Sai's BioSciences
Research Institute Pvt. Ltd.

CERTIFICATE

This is to certify that Mr. **M.D.Vaishnava Murari**, M.Tech-Biotechnology of Kumaraguru College of Technology, Coimbatore, has carried out his project for a period of 6 months (Nov-2009 to April-2010) and successfully completed the project work entitled "**BIOLOGICAL DATABASE CREATION OF PROTEIN METABOLIC DISORDERS**" under the guidance of Ms.B.SaiPriya at Sai's Biosciences Research Institute, Coimbatore.

Sai's BioSciences Research Institute Pvt. Ltd. SBRI Coimbatore

(Saipriya Balasubramanian)

Signature of the Guide
Sai's Bioscience Research
Institute Pvt.Ltd.
Coimbatore-4

Declaration

DECLARATION

I affirm that the project work titled **Biological Database Creation of Protein Metabolic Disorders** being submitted in partial fulfilment for the award of **M.Tech (Biotechnology)** is the original work carried out by me. It has not formed the part of any other project work submitted for award of any degree or diploma, either in this or any other University.

M.D.Vaishnava Murari

0820203015

I certify that the declaration made by the above candidate is true.

Signature of the Guide,

Dr.P.Ramalingam

Assistant Professor

Department of Biotechnology

Kumaraguru College of Technology

Coimbatore

Acknowledgement

ACKNOWLEDGEMENT

I am very much grateful to my **Parents** and the **Almighty** for showering their blessings on me without which none of these would have been possible.

I wish to extend my sincere thanks to our principal **Dr.S.Ramachandran** and for their incredible support for all my toil regarding the project.

With immense pleasure, I wish to avail this opportunity and evoke on record the ineffable personal indebtness and deep sense of gratitude to **Dr.S.Sadasivam, Dean-** Department of Biotechnology, Kumaraguru College of Technology, Coimbatore for giving me an opportunity to carry out my project work outside the campus.

I would like to thank and express my gratitude to my internal guide **Dr.P.Ramalingam, Assistant Professor,** Department of Biotechnology and all the staff members of Department of Biotechnology, Kumaraguru College of Technology, Coimbatore for their valuable suggestions and guidance.

I am elated to accord my deep sense of gratitude to **Ms.Saipriya Balasubramaniam** and other faculty members of Sai Bioscience's Research Institute- Coimbatore for their meticulous guidance, continuous encouragement and suggestions rendered throughout my project work.

It gives me immense pleasure to express my sincere thanks to **Dr.N.Saraswathy, Assistant professor,** Department of Biotechnology, Kumaraguru College of Technology and my special thanks to Mr.N.Krishnanand and Ms.R.Ramya and my beloved brother and my friends who were the pillars of support during the hardships of my project.

I am greatly indebted to **Dr.R.Baskar, Associate professor,** Department of Biotechnology, Kumaraguru College of Technology for his encouragement to carry out the project from the starting itself.

M.D.Vaishnava Murari

M.D.VAISHNAVA MURARI

Table of Contents

TABLE OF CONTENTS

Abstract

ABSTRACT

Metabolic disorders like Albinism, Alkaptonuria, Cystinosis, Cystinuria, Glycinuria, Hartnup's disease, Histidinemia, Maple syrup urine disease, Phenylketonuria, Tyrosinemia, etc are caused due to the lack or deficiency of amino acids which leads to serious medical consequences. The collection of clinically required data for these disorders requires laborious and manual literature searches In the present study, database of aminoacid deficiency diseases and compendium of aminoacid deficiency diseases (A^2D^2) were developed that covers clinical, genomic, reference and the important attributes of disorders that were found in humans. Entries are linked to their respective chromosomal location in the Online Mendelian Inheritance in Man (OMIM). This database is implemented in WAMP (Windows Apache Mysql PHP) platform. Also the database serves as a robust prototype for cataloging variation and disorder information between human and other species.

List of Figures

LIST OF FIGURES

List of Abbreviations

LIST OF ABBREVIATIONS

A^2D^2DB	Amino acid deficiency disorder database
OMIM	Online Mendelian inheritance in Man
EMBL	European Molecular Biology Laboratory
Unigene	Unique Gene
Ref Seq	Reference Sequences
HGO	Homogentisic acid oxydase gene
CSF	Cerebrospinal fluid
MSUD	Maple syrup urine disease
PKU	Phenylketonuria
PAH	Phenylalanine hydroxylase
GPCR	G-Protein coupled receptor
SPF	Sun protection factor
HGD	Homogentisate 1,2-dioxygenase
ESWL	Extracorporeal shock wavelithotripsy
BCKDH	Branched-chain alpha-keto acid dehydrogenase
HPD	4-hydroxyphenylpyruvate dioxygenase
NTBC	2(2-nitro-4-trifluoromethylbenzoyl)-1, 3-cyclohexanedione

SQL	Sequence Query language
NCBI	National Centre for Biotechnology Information
NLM	National library of medicine
NIH	National institute of health
EBI	European Bioinformatics Institute
UCSC	University of California, Santa Cruz
SIB	Swiss Institute of Bioinformatics
PIR	Protein Information Resource
Expasy	Expert Protein Analysis system
NBRF	National Biomedical Research foundation
WAMP	Windows Apache MySQL PHP
HTML	Hyper Text Markup Language

CHAPTER- 1

Introduction

1. INTRODUCTION

Biological databases are libraries of life sciences information, collected from scientific sciences information, scientific experiments, published literature, high throughput experiment technology, and computational analyses. Relational database concepts of computer science and Information retrieval concepts of digital libraries are important for understanding biological databases.

The diseases associated with protein abnormalities include those associated with increased production of proteins, decreased production of proteins, production of abnormal proteins, and excretion of unusual amounts of amino acids. A decrease in the amount of protein (hypoproteinemia) can result from a lack of amino acids for protein synthesis, a metabolic block, or other interference with normal protein synthesis. Increased excretion of protein, particularly in chronic renal disease with a loss of albumin in the urine (albuminuria), is another common cause of hypoproteinemia.

A group with abnormal protein metabolism is associated with a change in particular amino acids resulting either from an overflow mechanism, where the concentration of amino acids in the serum surpasses the renal threshold of the glomerular membrane, or from defective absorption of amino acids in renal tubules. Tyrosine appears to be one of the most critical amino acids, and its metabolism is related to four key diseases including phenylketonuria, hypothyroidism, albinism, and alkaptonuria. The liver plays a major role in the deamination of amino acids. Advanced hepatitis and cirrhosis may lead to increased levels of amino acids in the blood and excretion in the urine. Other diseases with amino aciduria that are believed to be the result of defective kidney function include cystinuria (the failure to reabsorb cystine, lysine, arginine, and ornithine), Wilson's disease (a degeneration involving copper metabolism in the liver and brain), Fanconi's syndrome, galactosemia, scurvy, rickets, and lead, cresol, or benzene poisoning.

1.1 Need of A^2D^2DB

Even though user community can obtain require information about the protein metabolic disorders, it take enormous time to search the data as presently the information are not digitized and are available in scattered literature. The protein metabolic disorders information is distributed among several organizations and individuals, which makes it difficult to access information about them easily and efficiently. So the easiest way is to create a web based online database to access and retrieve the information about required diseases level.

1.2 Problems in Data collection

The biological information contained in print media, in outdated electronic form and in modern databases constitutes an intellectual wealth produced by decades and centuries of research and considerable societal investment (Shanmughavel, 2007) however, the information is scattered in many sites and literature so user cannot get the correct information unless published literatures are correct.

1.3 How A^2D^2DB could help

A^2D^2DB is an online accessible database. It will give information about the Protein metabolic disorders, classification, symptoms, prevalence, pathophysiology, diagnosis & treatment. Other pleasant feature of this database is that it has link with OMIM, Entrez, EMBL, UNIGENE, ENSEMBL, UNIPROT, REF SEQ, INTERPRO, PFAM, and PRODOM so researchers/user can easily get the properties and particular about the diseases. The Disease browser is included. It would help anyone who wishes to know information about various protein information about the particular diseases.

1.4 Data's in A^2D^2DB

The first step in A^2D^2DB is documentation based on the availability of information about each metabolic disorder. So protein metabolic disorders information collected from various literatures and online databases and various web sites.

Amino acid Deficiency Disorder Database (A^2D^2DB) contains data's about the protein metabolic disorders of which its

- ✓ Disorder name
- ✓ Classification
- ✓ Signs & symptoms
- ✓ Prevalence
- ✓ Pathophysiology
- ✓ Diagnosis
- ✓ Treatment
- ✓ Protein information of the disorders
- ✓ Bibliography sources of the data used in the database

1.5 Metabolic disorders

Inborn errors of metabolism comprise a large class of genetic diseases involving disorders of metabolism. The majority are due to defects of single genes that code for enzymes that facilitate conversion of various substances (substrates) into others (products). In most of the disorders, problems arise due to accumulation of substances which are toxic or interfere with normal function, or to the effects of reduced ability to synthesize essential compounds. Inborn errors of metabolism are now often referred to as congenital metabolic diseases or inherited metabolic diseases, and these terms are considered synonymous.

The term **"inborn error of metabolism"** was coined by a British physician, Archibald Garrod (1857-1936), in the early 20th century (1908). He is known for work that prefigured the "one gene, one enzyme" hypothesis, based on his studies on the nature and inheritance of alkaptonuria. His seminal text, Inborn Errors of Metabolism was published in 1923.

1.5.1 Albinism

The word "albinism" refers to a group of inherited conditions. The term albinism comes from the Latin word albus, which means white, and, in 1908, Garrod first scientifically described it. The condition is known to affect all vertebrates, including humans. While the most common term for an organism affected by albinism is "albino" (noun and adjective), the word is sometimes used in derogatory ways towards people; more neutral terms are "albinistic" (adjective) and "person with albinism" (noun). Additional clinical adjectives sometimes used to refer to animals are "albinoid" and "albinic". People with albinism have little or no pigment in their eyes, skin, or hair. They have inherited altered genes that do not make the usual amounts of a pigment called melanin. One person in 17,000 in the U.S.A. has some type of albinism. Albinism affects people from all races. Most children with albinism are born to parents who have normal hair and eye color for their ethnic backgrounds. A common myth is that people with albinism have red eyes. In fact there are different types of albinism and the amount of pigment in the eyes varies. Although some individuals with albinism have reddish or violet eyes, Most have blue eyes. Some have hazel or brown eyes. However, all forms of albinism are associated with vision problems. Most forms of albinism are the result of the biological inheritance of genetically recessive alleles (genes) passed from both parents of an individual, though some rare forms are inherited from only one parent. There are other genetic mutations which are proven to be associated with albinism. All alterations, however, lead to changes in melanin production in the body. Albinism was formerly categorized as tyrosinase-positive or -negative. In cases of tyrosinase-positive albinism, the enzyme tyrosinase is present. The melanocytes (pigment cells) are unable to produce melanin for any one of a variety of reasons that do not directly involve the tyrosinase enzyme. In tyrosinase-negative cases, either the tyrosinase enzyme is not produced or a nonfunctional version is produced. This classification has been rendered obsolete by recent research.

1.5.2 Alkaptonuria

Alkaptonuria (Black urine disease or Alcaptonuria) is a rare inherited genetic disorder of phenylalanine and tyrosine metabolism. This is an autosomal recessive condition that is due to a defect in the enzyme homogentisate 1,2-dioxygenase (EC 1.13.11.5), which participates in the degradation of tyrosine. As a result, a toxic tyrosine byproduct called homogentisic acid (or alkapton) accumulates in the blood and is excreted in urine in large amounts (hence "-uria"). Excessive homogentisic acid causes damage to cartilage (ochronosis, leading to osteoarthritis) and heart valves as well as precipitating as kidney stones. Treatment with nitisinone, which suppresses homogentisic acid production, is being studied. Alkaptonuria is more common in Slovakia and the Dominican Republic than in other countries. In Slovakia the disease occurs in 1:19,000 people. In other ethnic groups, the normal prevalence is between 1:100,000 and 1:250,000. It is reported frequently in the Dominican Republic, but exact prevalence there is not known. The homogentisic acid oxidase gene (HGO) is found on chromosome 3q21–q23 spanning 60 kb and encompassing 14 exons. A number of single nucleotide changes, insertions, deletions, and mutations in introns have been identified in alkaptonuric patients. In all, mutations have been found in 11 of the 14 exons of the HGO gene.

1.5.3 Cystinosis

Cystinosis is a lysosomal storage disease in which the body accumulates the amino acid cystine (a building block of proteins) within cells. Excess cystine forms crystals that can build up and damage cells. These crystals negatively affect many systems in the body, especially the kidneys and eyes. It is a genetic disorder that typically follows an autosomal recessive inheritance pattern. Cystinosis is the most common cause of Fanconi syndrome in the pediatric age group. Fanconi syndrome occurs when the function of cells in renal tubules are impaired, leading to abnormal amounts of carbohydrates and amino acids in the urine, excessive urination, and low blood levels of potassium and phosphates.

1.5.4 Cystinuria

Cystinuria is an inherited metabolic disorder characterized by the abnormal movement (transport) in the intestines and kidneys, of certain organic chemical compounds (amino acids). These include cystine, lysine, arginine, and ornithine. Excessive amounts of undissolved cystine in the urine (cystinuria) cause the formation of stones (Calculi) in the kidney, bladder, and/or ureter. About one in every 10,000 people has cystinuria. Cystine stones are most common in young adults under age 40. Less than 3% of urinary tract stones are cystine stones. One of the peculiar things about cystinuria is that the amount of cystine excreted by the kidneys is not always related to the number and size of the stones formed. Some people with very high cystine levels form very few, if any stones. Others with comparatively low cystine levels are prolific stone formers.

1.5.5 Glycinuria

Iminoglycinuria, sometimes called familial iminoglycinuria, is an autosomal recessive disorder of renal tubular transport affecting reabsorption of the amino acid glycine, and the imino acids proline and hydroxyproline. This results in excess urinary excretion of all three acids ("-uria" denotes "in the urine"). Iminoglycinuria is a rare and complex disorder, associated with a number of genetic mutations which cause defects in both renal and intestinal transport systems of glycine and imino acids.

Imino acids typically contain an imine functional group, instead of the amino group found in amino acids. Proline is considered and usually referred to as an amino acid but unlike others, it has a secondary amine. This feature, unique to proline, identifies proline also as an imino acid. Hydroxyproline is another imino acid, made from the naturally-occurring hydroxylation of proline.

1.5.6 Hartnup's Disease

Hartnup disease, or Hartnup disorder, is an autosomal recessive metabolic disorder affecting the absorption of neutral amino acids (particularly tryptophan that can

be, in turn, converted into Serotonin, Melatonin and Niacin). Niacin is a precursor to nicotinamide, a necessary component of NAD+.

The causative gene, SLC6A19, is located on Chromosome 5.

1.5.7 Histidinemia

Histidinemia, also referred to as histidinuria, is a rare autosomal recessive metabolic disorder caused by a deficiency of the enzyme histidase. Histidase is needed for the metabolism of the amino acid histidine.

- Increased concentrations of Histidine in blood, urine and cerebrospinal fluid (CSF)
- Increased concentrations of Histidine in the metabolites of urine.
- Decreased concentrations of urocanic acid in blood and skin.

1.5.8 Maple Syrup Urine Disease

Maple Syrup Urine disease (MSUD), also called branched-chain ketoaciduria, is an autosomal recessive metabolic disorder affecting branched-chain amino acids. It is one type of organic acidemia. The condition gets its name from the distinctive sweet odor of affected infants' urine.

1.5.9 Phenylketonuria

Phenylketonuria (PKU) is an inherited error of metabolism caused by a deficiency in the enzyme phenylalanine hydroxylase. Loss of this enzyme results in mental retardation, organ damage, and unusual posture and can, in cases of maternal PKU, severely compromise pregnancy. Classical PKU is an autosomal recessive disorder, caused by mutations in both alleles of the gene for phenylalanine hydroxylase (PAH), found on chromosome 12. In the body, phenylalanine hydroxylase converts the amino acid phenylalanine to tyrosine, another amino acid. Mutations in both copies of the gene for PAH mean that the enzyme is inactive or is less efficient, and the concentration of

phenylalanine in the body can build up to toxic levels. In some cases, mutations in PAH will result in a phenotypically mild form of PKU called hyperphenylalanemia. Both diseases are the result of a variety of mutations in the PAH locus; in those cases where a patient is heterozygous for two mutations of PAH (i.e., each copy of the gene has a different mutation), the milder mutation will predominate.

The incidence of PKU is about 1 in 15,000 births, but the incidence varies widely in different human populations from 1 in 4,500 births among the population of Ireland to 1 in 13,000 births in Norway to fewer than one in 100,000 births among the population of Finland. Turkey, at 1 in 2600, has the highest incidence rate in the world. The illness is also more common in Italy and China, as well as in Yemeni populations.

1.5.10 Tyrosinemia

Tyrosinemia (or "Tyrosinemia") is an error of metabolism, usually inborn, in which the body cannot effectively break down the amino acid tyrosine. Symptoms include liver and kidney disturbances and mental retardation. Most inborn forms of tyrosinemia produce hypertyrosinemia (high levels of tyrosine).

CHAPTER- II

Objective of the Study

2. OBTECTIVES OF THE STUDY

The present study is to carry out with the following objectives:

- To create the database for the Amino acid Deficiency Disorders (A^2D^2) containing information about the disease types with various properties and protein information from the SWISSPROT Database.
- To create the database using MySQL.
- To create an interface that enables the user to retrieve data using PHP.
- To retrieve information, the user can enter the name of the disease by clicking search button from Amino acid Deficiency Disorder Database (A^2D^2DB) home page.

CHAPTER- III

Review of Literature

3. REVIEW OF LITERATURE

3.1 Metabolic Disorders

A metabolic disorder is a medical disorder which affects the production of energy within individual human (or animal) cells. Most metabolic disorders are genetic, though a few are "acquired" as a result of diet, toxins, infections, etc. Genetic metabolic disorders are also known as inborn errors of metabolism.

In general, the genetic metabolic disorders are caused by genetic defects that result in missing or improperly constructed enzymes necessary for some step in the metabolic process of the cell.

3.2 Protein Metabolic Disorders

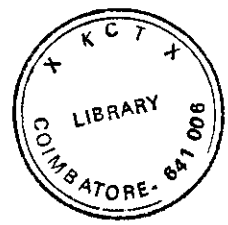
Amino acids are the building blocks of proteins and have many functions in the body. Hereditary disorders of amino acid processing can result from defects either in the breakdown of amino acids or in the body's ability to get amino acids into cells. Because these disorders cause symptoms early in life, newborns are routinely screened for several common ones. In the United States, newborns are commonly screened for Phenylketonuria, Maple syrup urine disease, Homocystinuria, Tyrosinemia, and a number of other inherited disorders, although screening varies from state to state. Everyone with one of these inherited metabolic disorders must have a specific diet, planned in accordance their metabolic tolerance. The diet must be supervised by a qualified nutritionist or physician knowledgeable about the condition, and must be monitored regularly through blood tests.

Treatment of these disorders is accomplished with dietary restriction of the offending amino acid(s) and sometimes medication. Urea cycle disorders will require treatment with low protein diets and medications to prevent hyperammonemia and remove toxic compounds. Infants with neonatal presentations of a urea cycle disorders

represent medical emergencies and outcomes may be variable. These patients typically require aggressive treatment with hemodialysis.

The Protein Metabolic Disorders includes

- Albinism
- Alkaptonuria
- Cystinosis
- Cystinuria
- Glycinuria
- Hartnup's Disease
- Histidinemia
- Maple Syrup Urine
- Phenylketonuria
- Tyrosinemia



3.3 Albinism

3.3.1 Introduction

The word "albinism" refers to a group of inherited conditions. The term albinism comes from the Latin word albus, which means white, and, in 1908, Garrod first scientifically described it. The condition is known to affect all vertebrates, including humans. While the most common term for an organism affected by albinism is "albino" (noun and adjective), the word is sometimes used in derogatory ways towards people; more neutral terms are "albinistic" (adjective) and "person with albinism" (noun). Additional clinical adjectives sometimes used to refer to animals are "albinoid" and "albinic". People with albinism have little or no pigment in their eyes, skin, or hair. They have inherited altered genes that do not make the usual amounts of a pigment called melanin. One person in 17,000 in the U.S.A. has some type of albinism. Albinism affects people from all races. Most children with albinism are born to parents who have normal hair and eye color for their ethnic backgrounds. A common myth is that people with

albinism have red eyes. In fact there are different types of albinism and the amount of pigment in the eyes varies. Although some individuals with albinism have reddish or violet eyes, Most have blue eyes. Some have hazel or brown eyes. However, all forms of albinism are associated with vision problems. Most forms of albinism are the result of the biological inheritance of genetically recessive alleles (genes) passed from both parents of an individual, though some rare forms are inherited from only one parent. There are other genetic mutations which are proven to be associated with albinism. All alterations, however, lead to changes in melanin production in the body. Albinism was formerly categorized as tyrosinase-positive or -negative. In cases of tyrosinase-positive albinism, the enzyme tyrosinase is present. The melanocytes (pigment cells) are unable to produce melanin for any one of a variety of reasons that do not directly involve the tyrosinase enzyme. In tyrosinase-negative cases, either the tyrosinase enzyme is not produced or a nonfunctional version is produced. This classification has been rendered obsolete by recent research.

3.3.2 Classification

There are two main categories of albinism in humans:

- In oculocutaneous albinism (despite its Latin-derived name meaning "eye-and-skin" albinism), pigment is lacking in the eyes, skin and hair. (The equivalent mutation in non-humans also results in lack of melanin in the fur, scales or feathers.) People with oculocutaneous albinism can have anywhere from no pigment at all to almost-normal levels.

- In ocular albinism, only the eyes lack pigment. People who have ocular albinism have generally normal skin and hair color, although it is typically lighter than either parent. Many even have a normal eye appearance.

Other conditions include albinism as part of their presentation. These include Hermansky-Pudlak syndrome, Chediak-Higashi syndrome, Griscelli syndrome, Waardenburg syndrome, and Tietz syndrome. These conditions are sometimes classified

with albinism. Several have sub-types. Some are easily distinguished by appearance, but in most cases genetic testing is the only way to be certain.

3.3.3 Symptoms

Patients with albinism usually present in early infancy and generally will have any of the following symptoms:

- Skin, hair, and eye discoloration are caused by abnormalities of melanin metabolism. However, this might not be as obvious in patients with ocular albinism.

Eye conditions common in albinism may include:

- Nystagmus, irregular rapid movement of the eyes back and forth, or in circular motion.
- Strabismus, eye misalignment ("crossed eyes" or "lazy eye").
- Refractive errors such as myopia or hyperopia and especially astigmatism are more likely
- Photophobia, hypersensitivity to bright light and glare.
- Macular hypoplasia, underdevelopment of the fovea, the center of the retina
- Optic nerve hypoplasia, underdevelopment of the optic nerve
- Abnormal decussation (crossing) of the optic nerve fibers in the optic chiasm
- Amblyopia, decrease in acuity of one or both eyes due to poor transmission to the brain, often due to other conditions such as strabismus.

3.3.4 Pathophysiology

Albinism occurs when one of several genetic defects makes the body unable to produce or distribute melanin, a natural substance that gives color to your hair, skin, and iris of the eye. Melanin is the pigment responsible for skin, hair, and eye coloration. Albinism is caused by a disorder of melanin metabolism, and the defect can lie with

either melanin synthesis or distribution. Melanin is synthesized in melanocytes from the amino acid tyrosine. This process takes place in special organelles called melanosomes. The pathophysiology of oculocutaneous albinism involves a reduction in the amount of melanin present in each of the melanosomes. The pathophysiology of ocular albinism is a reduction in the number of melanosomes, although each melanosome may be fully pigmented. The most important enzyme in the synthesis of melanin is tyrosinase, which converts tyrosine to dopa. The gene for the enzyme tyrosinase has been localized to chromosome 11. A number of mutations have been found at this locus, which can result in an absent or defective tyrosinase enzyme. This results in type I oculocutaneous albinism, which is characterized by complete absence of skin and eye pigmentation, despite a normal number of melanosomes.

In contrast, the type II (tyrosine positive) oculocutaneous albinism defect is within the P polypeptide, which is a melanosomal tyrosine transporter. The P gene has been mapped to chromosome 15 and is more commonly linked with albinism in patients of African descent. These patients do have some pigment, but they have lighter pigmentation than expected due to their relatives and ethinicity. Ocular albinism type I is an X-linked disorder related to defects in the OA1 gene. This gene produces pigment cell-specific, intracellular G-protein coupled receptor (GPCR), which appears to result in faulty transport of melanosomes and lysosomes as well as macromelanosomes. Patients with this disorder are found to have giant melanosomes in their skin melanocytes and retinal pigment epithelium.

3.3.5 Treatment

The goal of treatment is to relieve symptoms. Treatment depends on the severity of the disorder. Treatment involves protecting the skin and eyes from the sun:

- Reduce sunburn risk by avoiding the sun, using sunscreen, and covering up completely with clothing when exposed to the sun.
- Sunscreen should have a high sun protection factor (SPF).
- Sunglasses (UV protected) may relieve light sensitivity.

3.4 Alkaptonuria

3.4.1 Introduction

Alkaptonuria (black urine disease or alcaptonuria) is a rare inherited genetic disorder of phenylalanine and tyrosine metabolism. This is an autosomal recessive condition that is due to a defect in the enzyme homogentisate 1,2-dioxygenase (EC 1.13.11.5), which participates in the degradation of tyrosine. As a result, a toxic tyrosine byproduct called homogentisic acid (or alkapton) accumulates in the blood and is excreted in urine in large amounts (hence -uria). Excessive homogentisic acid causes damage to cartilage (ochronosis, leading to osteoarthritis) and heart valves as well as precipitating as kidney stones. Treatment with nitisinone, which suppresses homogentisic acid production, is being studied.

Alkaptonuria is more common in Slovakia and the Dominican Republic than in other countries. In Slovakia the disease occurs in 1:19,000 people. In other ethnic groups, the normal prevalence is between 1:100,000 and 1:250,000. It is reported frequently in the Dominican Republic, but exact prevalence there is not known. The homogentisic acid oxidase gene (HGO) is found on chromosome 3q21–q23 spanning 60 kb and encompassing 14 exons. A number of single nucleotide changes, insertions, deletions, and mutations in introns have been identified in alkaptonuric patients. In all, mutations have been found in 11 of the 14 exons of the HGO gene.

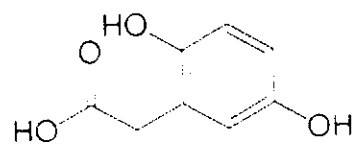


Figure 3.4.1 Structure of Homogentisic acid

3.4.2 Signs & Symptoms

Alkaptonuria is often asymptomatic, but the sclera of the eyes may be pigmented (often only at a later age), and the skin may be darkened in sun-exposed areas and around sweat glands; sweat may be coloured brown. Urine may turn brown if collected and left exposed to open air, especially when left standing for a period of time. Kidney stones and stone formation in the prostate (in men) are common and may occur in more than a quarter of cases. The main symptoms of alkaptonuria are due to the accumulation of homogentisic acid in tissues. In the joints this leads to cartilage damage, specifically in the spine, leading to low back pain at a young age in most cases. Cartilage damage may also occur in the hip and shoulder. Joint replacement surgery (hip and shoulder) is often necessary at a relatively young age. Valvular heart disease, mainly calcification and regurgitation of the aortic and mitral valves, may occur, and in severe and progressive cases valve replacement may be necessary. Coronary artery disease may be accelerated in alkaptonuria. A distinctive characteristic of alkaptonuria is that ear wax exposed to air turns red or black (depending on diet) after several hours because of the accumulation of homogentisic acid.

3.4.3 Pathophysiology

Homogentisic acid is a natural intermediary of the metabolism of tyrosine, an amino acid. Hepatic homogentisate 1, 2-dioxygenase (coded by the HGD gene) metabolizes homogentisic acid into 4-maleylacetoacetate. Alkaptonuria arises in people who have inherited two abnormal HGD genes: one from each parent. Numerous different HGD mutations have been identified. In a patient who underwent a liver transplant for an unrelated problem, alkaptonuria resolved and joint disease stabilized after the transplant, confirming that the liver is the main site of homogentisic acid production in alkaptonuria.

3.4.4 Diagnosis

The diagnosis of alkaptonuria needs to be suspected before diagnostic testing can be performed using paper chromatography and thin layer chromatography. Both blood plasma and urine can be used for diagnosis. In healthy subjects, homogentisic acid is absent in both blood plasma and urine. In alkaptonuria, plasma levels are 6.6 micrograms/ml on average, and urine levels are on average 3.12 mmol/mmol of creatinine.

A urine test (urinalysis) is done to test for alkaptonuria. If ferric chloride is added to the urine, it will turn the urine a black color in patients with this condition.

3.4.5 Treatment

No treatment modality has been unequivocally demonstrated to reduce the complications of alkaptonuria. Commonly recommended treatments include dietary restriction of phenylalanine and tyrosine and large doses of ascorbic acid (vitamin C). Dietary restriction may be effective in children, but benefits in adults have not been demonstrated. The insecticide nitisinone inhibits 4-hydroxyphenylpyruvate dioxygenase, the enzyme that generates homogentisic acid from 4-hydroxyphenylpyruvic acid. This reduces homogentisic acid. The main side-effect is irritation of the cornea. and there is a concern that it will cause the symptoms of hereditary tyrosinaemia type III because of the possible accumulation of tyrosine or other intermediaries. Further studies are being conducted.

3.5 Cystinosis

3.5.1 Introduction

Cystinosis is a lysosomal storage disease in which the body accumulates the amino acid cystine (a building block of proteins) within cells. Excess cystine forms crystals that can build up and damage cells. These crystals negatively affect many

systems in the body, especially the kidneys and eyes. It is a genetic disorder that typically follows an autosomal recessive inheritance pattern. Cystinosis is the most common cause of Fanconi syndrome in the pediatric age group. Fanconi syndrome occurs when the function of cells in renal tubules are impaired, leading to abnormal amounts of carbohydrates and amino acids in the urine, excessive urination, and low blood levels of potassium and phosphates.

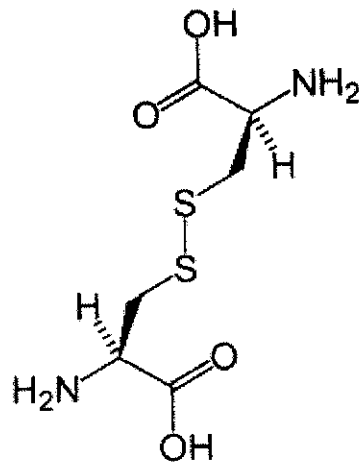


Figure 3.5.1 Structure of Cystine skeleton

3.5.2 Classification

There are three distinct types of cystinosis.

- Infantile nephropathic
- Adolescent nephropathic
- Adult non-nephropathic

In order of decreasing severity, they are nephropathic cystinosis, intermediate cystinosis, and non-nephropathic or ocular cystinosis. Infants affected by nephropathic cystinosis initially exhibit poor growth and a particular type of kidney damage (renal Fanconi syndrome) that causes the kidneys to eliminate certain molecules that should be reabsorbed into the bloodstream. The kidney problems lead to the loss of important minerals, salts, fluids, and other nutrients. The loss of nutrients impairs growth and may

result in soft, bowed bones (hypophosphatemic rickets), especially in the legs. The nutrient imbalances in the body lead to increased urination, thirst, dehydration, and abnormally acidic blood (acidosis). By about the age of 2, cystine crystals may be present in the clear covering of the eye (cornea). The buildup of these crystals in the eye causes an increased sensitivity to light (photophobia). Untreated children will experience complete kidney failure by about the age of 10. Other signs and symptoms that may occur in untreated people, especially after adolescence, include muscle deterioration, blindness, inability to swallow, diabetes, and thyroid and nervous system problems.

3.5.3 Symptoms

There are three distinct types of cystinosis each with slightly different symptoms: nephropathic cystinosis, intermediate cystinosis, and non-nephropathic or ocular cystinosis. Infants affected by nephropathic cystinosis initially exhibit poor growth and particular kidney problems (sometimes called renal Fanconi syndrome). The kidney problems lead to the loss of important minerals, salts, fluids, and other nutrients. The loss of nutrients not only impairs growth, but may result in soft, bowed bones (hypophosphatemic rickets), especially in the legs. The nutrient imbalances in the body lead to increased urination, thirst, dehydration, and abnormally acidic blood (acidosis).

By about age two, cystine crystals may also be present in the cornea. The buildup of these crystals in the eye causes an increased sensitivity to light (photophobia). Without treatment, children with cystinosis are likely to experience complete kidney failure by about age ten. Other signs and symptoms that may occur in untreated patients include muscle deterioration, blindness, inability to swallow, diabetes, and thyroid and nervous system problems.

The signs and symptoms of intermediate cystinosis are the same as nephropathic cystinosis, but they occur at a later age. Intermediate cystinosis typically begins to affect individuals around age twelve to fifteen. Malfunctioning kidneys and corneal crystals are the main initial features of this disorder. If intermediate cystinosis is left untreated, complete kidney failure will occur, but usually not until the late teens to mid twenties.

People with non-nephropathic or ocular cystinosis do not usually experience growth impairment or kidney malfunction. The only symptom is photophobia due to cystine crystals in the cornea.

3.5.4 Diagnosis

Cystinosis is a rare genetic disorder that causes an accumulation of the amino acid cystine within cells, forming crystals that can build up and damage the cells. These crystals negatively affect many systems in the body, especially the kidneys and eyes.

The accumulation is caused by abnormal transport of cystine from lysosomes, resulting in a massive intra-lysosomal cystine accumulation in tissues. Via an as yet unknown mechanism, lysosomal cystine appears to amplify and alter apoptosis in such a way that cells die inappropriately, leading to loss of renal epithelial cells. These results in renal Fanconi syndrome, and similar loss in other tissues can account for the short stature, retinopathy, and other features of the disease.

Definitive diagnosis and treatment monitoring are most often performed through measurement of white blood cell cystine level using tandem mass spectrometry.

3.5.5 Genetics

Cystinosis occurs due to a mutation in the gene CTNS, located on chromosome 17, which codes for cystinosin, the lysosomal cystine transporter. Symptoms are first seen at about 3 to 18 months of age with profound polyuria (excessive urination), followed by poor growth, photophobia, and ultimately kidney failure by age 6 years in the nephropathic form.

All forms of cystinosis (nephropathic, juvenile and ocular) are autosomal recessive, which means that the trait is located on an autosomal gene, and an individual who inherits two copies of the gene (one from both parents) will have the disorder. There is a 25% risk of having a child with the disorder, when both parents are carriers of an autosomal recessive trait.

Cystinosis affects approximately 1 in 100,000 to 200,000 newborns. and there are only around 2,000 known individuals with cystinosis in the world. The incidence is higher in the province of Brittany, France, where the disorder affects 1 in 26,000 individuals.

3.5.6 Treatment

Cystinosis is normally treated with a drug called cysteamine (brand name Cystagon). The administration of cysteamine can reduce the intracellular cystine content. Cysteamine concentrates inside the lysosomes and reacts with cystine to form both cysteine and a cysteine-cysteamine complex, which are able to leave the lysosomes. When administered regularly, cysteamine decreases the amount of cystine stored in lysosomes and correlates with conservation of renal function and improved growth. Cysteamine eyedrops remove the cystine crystals in the cornea that can cause photophobia if left unchecked. Patients with cystinosis are also often given sodium citrate to treat the blood acidosis, as well as potassium and phosphorus supplements.

3.6. Cystinuria

3.6.1 Introduction

Cystinuria is an inherited metabolic disorder characterized by the abnormal movement (transport) in the intestines and kidneys, of certain organic chemical compounds (amino acids). These include cystine, lysine, arginine, and ornithine. Excessive amounts of undissolved cystine in the urine (cystinuria) cause the formation of stones (calculi) in the kidney, bladder, and/or ureter. About one in every 10,000 people has cystinuria. Cystine stones are most common in young adults under age 40. Less than 3% of urinary tract stones are cystine stones. One of the peculiar things about cystinuria is that the amount of cystine excreted by the kidneys is not always related to the number and size of the stones formed. Some people with very high cystine levels form very few, if any stones. Others with comparatively low cystine levels are prolific stone formers.

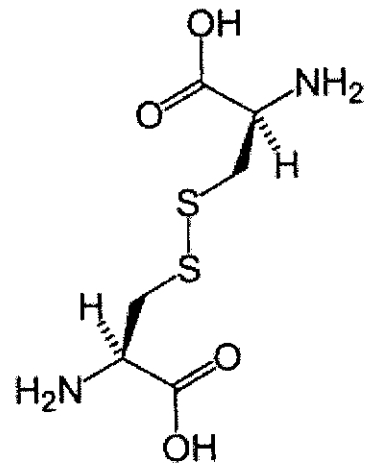


Figure 3.6.1 Cystine Structure

3.6.2 Signs & Symptoms

If you have a kidney stone that is persistent, you could have cystinuria. Cystinuria is a disorder of the kidneys where your body doesn't metabolize amino acids, the building blocks of protein. Cystinuria is kind of hard to diagnose, so someone could go a while without even knowing they have cystinuria. If not treated early enough, the patient could experience serious injury to the kidneys and to surrounding organs, or even death.

- Blood in the urine
- Flank pain or pain in the side or back
- Usually on one side; rarely felt on both sides
- Often severe
- May get increasingly worse over days
- Pain may also be felt in the pelvis, groin, genitals, or between the upper abdomen and the back.

3.6.3 Pathophysiology

Mutations in the SLC3A1 and SLC7A9 genes cause cystinuria. The SLC3A1 and SLC7A9 genes provide instructions for producing the two parts of a transporter protein

that is made primarily in the kidneys. These defects prevent proper reabsorption of basic or positively charged amino acids such as histidine, lysine, ornithine, arginine and cysteine.

Normally this protein allows certain amino acids, including cysteine, to be reabsorbed into the blood from the filtered fluid that will become urine. Mutations in either of these genes disrupt the ability of this transporter protein to reabsorb these amino acids, allowing them to become concentrated in the urine. As the levels of cysteine in the urine increase, the crystals typical of cystinuria are able to form, resulting in kidney stones. Cystine crystals form hexagonal-shaped crystals which can be viewed upon microscopic analysis of the urine. The other amino acids that are not reabsorbed do not create crystals in urine. The disorder affects 1 in 10,000 people, making it the most common genetic error of amino acid transport. Cystinuria is inherited in an autosomal recessive pattern.

3.6.4 Prevention

There is no known prevention for cystinuria. Any person with a known history of stones in the urinary tract should drink plenty of fluids to regularly produce a high amount of urine. This allows stones and crystals to leave the body before they become large enough to cause symptoms.

3.6.5 Treatment

The goal of treatment is to relieve symptoms and prevent the development of more stones. A person with severe symptoms may need to be admitted to a hospital. Treatment involves drinking plenty of fluids, particularly water, so that large amounts of urine are produced. The patient should drink at least 6-8 glasses per day. In some cases, fluids may need to be given through a vein (by IV). Medications may be prescribed to help dissolve the cystine crystals. Eating less salt can also decrease cystine excretion and stone formation. Pain relievers may be needed to control pain in the kidney or bladder

area associated with the passage of stones. The stones usually pass through the urine on their own. If they do not, surgery may be needed:

- Percutaneous nephrostolithotomy or nephrolithotomy
- Ureteroscopy, for stones in the lower urinary tract
- Extracorporeal shock wavelithotripsy (ESWL). This procedure is not as successful for removal of cystine stones as it is for other types of stones)

3.7 Glycinuria

3.7.1 Introduction

Iminoglycinuria, sometimes called familial iminoglycinuria,is an autosomal recessive disorder of renal tubular transport affecting reabsorption of the amino acid glycine, and the imino acids proline and hydroxyproline. This results in excess urinary excretion of all three acids ("-uria" denotes "in the urine"). Iminoglycinuria is a rare and complex disorder, associated with a number of genetic mutations which cause defects in both renal and intestinal transport systems of glycine and imino acids.

Imino acids typically contain an imine functional group, instead of the amino group found in amino acids. Proline is considered and usually referred to as an amino acid but unlike others, it has a secondary amine. This feature, unique to proline, identifies proline also as an imino acid. Hydroxyproline is another imino acid, made from the naturally-occurring hydroxylation of proline.

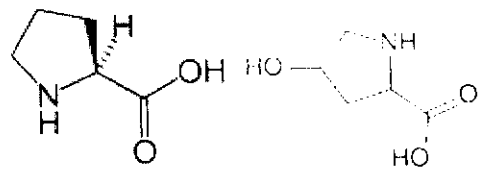


Figure 3.7.1 Structure of Proline & Hydroxyproline

3.7.2 Characteristics

The primary characteristic of iminoglycinuria is the presence of glycine and imino acids in the urine. Otherwise, it is thought to be a relatively benign disorder, although symptoms associated with disruptions of proline and glycine metabolism caused by malabsorption may be present with iminoglycinuria. These include encephalopathy, mental retardation, deafness, blindness, kidney stones, hypertension and gyrate atrophy.

Gyrate atrophy is an inherited degenerative disorder of the retina and choroid, sometimes accompanying the metabolic condition hyperornithinemia. The presence of gyrate atrophy with iminoglycinuria stems from a deficiency of proline in chorioretinal tissues, while processes behind hyperornithinemia disrupt the metabolic pathway from ornithine to proline, which alters the catabolism of ornithine, and also results in reduced levels of proline. Thus, gyrate atrophy can be found with either disorder, with proline deficiency as an underlying feature.

Hyperglycinuria is another disorder affecting reabsorption of glycine and imino acids, similar to iminoglycinuria and considered to be a heterozygous form. When accompanied by a specific type of kidney stone (nephrolithiasis), it is sometimes referred to as "iminoglycinuria, type II".

3.7.3 Pathophysiology

Glycine, proline and hydroxyproline share common renal tubular mechanisms of reabsorption, a function specific to the proximal tubule. Either reabsorption or absorption of glycine and imino acids takes place respectively at the proximal tubule or intestinal brush border epithelium. The more selective transport of proline and other imino acids is driven at the molecular level by a mammalian cellular transport mechanism aptly known as system IMINO.

While no single genetic mutation has been established as the cause of iminoglycinuria; several mutations, affecting transport mechanisms shared by glycine,

proline and hydroxyproline, as well as those which selectively transport either glycine or imino acids, including the IMINO system, are known to be associated with the disorder. When combined, these factors will result in a variable phenotype for iminoglycinuria depending on which mutations are present. However, despite the role that intestinal malabsorption of glycine and imino acids can play in iminoglycinuria, the primary defect disrupts their renal transport and reabsorption. This is evident, as inherited iminoglycinuria can be clinically present with no intestinal involvement.

In mammals, including humans, the transport of amino and imino acids from the lumen (interior) of the intestine or the renal proximal tubule into the cells occurs at the brush border membrane of the epithelium (moist, tightly-packed cellular lining of many tissues and organs of the body). Here, cotransporters such as sodium or chloride (part of the system of Na-K-Cl co transporters) couple with the amino or imino acids on the molecular level and transport them through specific integral membrane proteins that form ion channels, which are located within the cell membrane. From the cells, the absorbed or reabsorbed amino and imino acids eventually reach the blood. Absorption refers to the overall process happening in the intestine in lieu of normal digestive breakdown of proteins, while reabsorption refers to the process occurring in the renal proximal tubule to reclaim amino and imino acids that have been filtered out of the blood via the glomerulus.

These forms of transport require energy, as the products being transported are usually moving against a higher concentration gradient. This process, called active transport, get its energy from ATP and other ATP-related cotransport systems that produce energy, like the sodium-potassium pump.

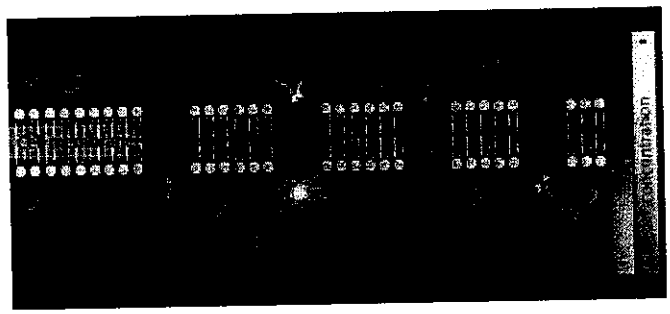


Figure 3.7.3 Active transport into a cell through ion channels, using the coupling power provided by sodium-potassium exchange.

3.7.4 Mechanism

The primary defect associated with iminoglycinuria is a homozygous (recessive) mutation of the SLC36A2 (PAT2) gene. One of several membrane transport proteins in the solute carrier family of amino acid transporters, PAT2 is the high-affinity renal transporter of glycine, proline and hydroxyproline found to be defective in both alleles when iminoglycinuria is present in an individual. This is in contrast to the fact that when only one PAT2 allele is defective, hyperglycinuria will be present instead of iminoglycinuria. These findings delineate iminoglycinuria as the homozygous form of hyperglycinuria, with the former having a higher degree of urinary excretion of glycine and imino acids correlating to mutations in both alleles.

Another mutation suspected to convey the iminoglycinuria phenotype may be found in the SLC36A1 (PAT1) gene. Identified as the low-affinity intestinal transporter of glycine and imino acids, PAT1 works in cooperation with the renal sodium-hydrogen exchanger NHE3 (SLC9A3). As absorption and reabsorption of glycine, proline and hydroxyproline occurs through PAT1 as well, it is believed to play another role in expressing the malabsorptive iminoglycinuria phenotype. Recent reports, however, suggest a more diminished role from PAT1 in some cases of the disorder.

While PAT2 is strongly indicated as the primary mutagen responsible for iminoglycinuria, the variability of the phenotype is found to be instituted by three

modifying genetic mutations. The major one among these is believed to be system IMINO.

Defined as the sodium-dependant proline transporter not inhibited by alanine, system IMINO, believed to be formed by the SLC6A20 (SIT1) gene, is a crucial mammalian transport mechanism responsible for both renal reabsorption and intestinal absorption of proline and other imino acids, such as hydroxyproline and pipecolate. The mRNA sequence for SIT1 is expressed in a great deal of the gastrointestinal tract, including the stomach, duodenum, jejunum, ileum, cecum and colon. It is also found in the kidney, optical choroid, and parts of the central nervous system such the brain and microglial cells.

Reduced penetrance is a phenomenon where a fully-inherited genetic trait, such as a disease or disorder, fails to exhibit the expected phenotype. This has been reported in some cases of iminoglycinuria. Here, system IMINO is thought to play a role in reduced penetrance of iminoglycinuria by compensating for imino acid malabsorption related specifically to mutations of PAT2.Conversely, SIT1 mutations are believed to result in full expression of iminoglycinuria in some cases where heterozygous mutations of PAT2 would otherwise have only been sufficient to cause hyperglycinuria.

Two other transport systems are believed to play subsequent roles in iminoglycinuria, when mutations in them are present. The neutral amino acid transporter SLC6A19 (affecting glycine, proline, and other neutral amino acids like cysteine and tryptophan), associated with Hartnup disease, plays a role in iminoglycinuria as a modifier to PAT2 mutations and is also directly affected by the actions of SIT1. The glycine-specific transporter, SLC6A18, also has an affect on the iminoglycinuria phenotype by either compounding or compensating for failures of glycine transport.

To summarize, iminoglycinuria is primarily expressed by homozygous mutations of the PAT2 renal transporter, while the overall iminoglycinuria phenotype may be modified by normal or defective activity of SIT1 (IMINO), SLC6A19 and SLC6A18.

3.7.5 Inheritance

Iminoglycinuria is believed to be inherited in an autosomal recessive manner. This means a defective gene responsible for the disorder is located on an autosome, and two copies of the defective gene (one inherited from each parent) are required in order to be born with the disorder. The parents of an individual with an autosomal recessive disorder both carry one copy of the defective gene, but usually do not experience any signs or symptoms of the disorder.

A non-inherited cause of excess urinary excretion of proline and glycine, similar to that found in iminoglycinuria, is quite common to newborn infants younger than 6 months. Sometimes referred to as neonatal iminoglycinuria, it is due to underdevelopment of high-affinity transport mechanisms within the renal circuit, specifically PAT2, SIT1 and SLC6A18. The condition corrects itself with age. In cases where this persists beyond childhood, however, inherited hyperglycinuria or iminoglycinuria may be suspected.

3.8 Hartnup's Disease

3.8.1 Introduction

Hartnup disease, or Hartnup disorder, is an autosomal recessive metabolic disorder affecting the absorption of neutral amino acids (particularly tryptophan that can be, in turn, converted into Serotonin, Melatonin and Niacin). Niacin is a precursor to nicotinamide, a necessary component of NAD+. The causative gene, SLC6A19, is located on Chromosome 5.

3.8.2 Symptoms

Hartnup disease manifest during infancy with variable clinical presentation: failure to thrive, photosensitivity, intermittent ataxia, nystagmus and tremor. Nicotinamide is necessary for neutral amino acid transporter production in the proximal

renal tubules found in the kidney, and intestinal mucosal cells found in the small intestine. Therefore, a symptom stemming from this disorder results in increased amounts of amino acids in the urine. Pellagra, a similar condition, is also caused by low nicotinamide; this disorder results in dermatitis, diarrhea and dementia.

Hartnup disease is a disorder of amino acid transport in the intestine and kidneys; otherwise, the intestine and kidneys function normally, and the effects of the disease occur mainly in the brain and skin. Symptoms may begin in infancy or early childhood, but sometimes they begin as late as early adulthood. Symptoms may be triggered by sunlight, fever, drugs, or emotional or physical stress. A period of poor nutrition nearly always precedes an attack. The attacks usually become progressively less frequent with age. Most symptoms occur sporadically and are caused by a deficiency of niacinamide. A rash develops on parts of the body exposed to the sun. Mental retardation, short stature, headaches, unsteady gait, and collapsing or fainting are common. Psychiatric problems (such as anxiety, rapid mood changes, delusions, and hallucinations) may also result.

3.8.3 Causes

Hartnup disease is inherited as an autosomal recessive trait. Heterozygotes are normal. Consanguinity is common. In 2004, a causative gene, SLC6A19, was located on band SLC6A19 is a sodium-dependent and chloride-independent neutral amino acid transporter, expressed predominately in the kidneys and intestine.

3.8.4 Diagnosis

The defective gene controls the absorption of certain amino acids from the intestine and the reabsorption of those amino acids in the kidneys. Consequently, a person with Hartnup disease cannot absorb amino acids properly from the intestine and cannot reabsorb them properly from tubules in the kidneys. Excessive amounts of amino acids, such as tryptophan, are excreted in the urine. The body is thus left with inadequate amounts of amino acids, which are the building blocks of proteins. With too little

tryptophan in the blood, the body is unable to make a sufficient amount of the B-complex vitamin Niacinamide, particularly under stress when more vitamins are needed.

3.8.5 Treatment

A high-protein diet can overcome the deficient transport of neutral amino acids in most patients. Poor nutrition leads to more frequent and more severe attacks of the disease, which is otherwise asymptomatic. Advise all patients who are symptomatic to use physical and chemical protection from sunlight. Avoiding excessive exposure to sunlight, wearing protective clothing, and using physical and chemical sunscreens are mandatory. Recommend sunscreens with a skin protection factor of 15 or greater. Advise patients to avoid other aggravating factors, such as photosensitizing drugs, as much as possible. In patients with niacin deficiency and symptomatic disease, daily supplementation with nicotinic acid or nicotinamide reduces both number and severity of attacks. Neurologic and psychiatric treatment is needed in patients with severe CNS involvement.

3.9 Histidinemia

3.9.1 Introduction

Histidinemia, also referred to as histidinuria, is a rare autosomal recessive metabolic disorder caused by a deficiency of the enzyme histidase. Histidase is needed for the metabolism of the amino acid histidine.

- Increased concentrations of Histidine in blood, urine and cerebrospinal fluid.
- Increased concentrations of Histidine in the metabolites of urine.
- Decreased concentrations of urocanic acid in blood and skin.

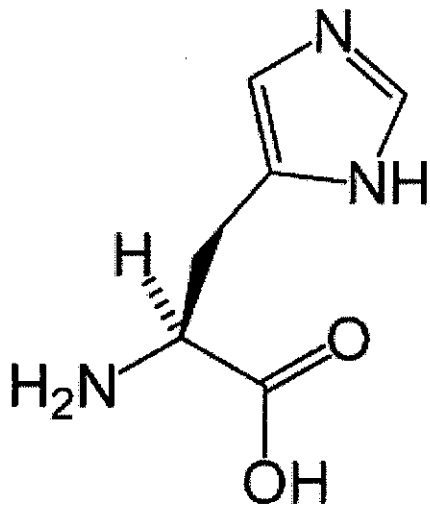


Figure 3.9.1 Structure of L-Histidine

3.9.2 Diagnosis & Symptoms

Histidenemia is characterized by increased levels of histidine, histamine and imidazole in blood, urine and cerebrospinal fluid. This also results in decreased levels of the metabolite urocanic acid in blood, urine, and skin cells.

Though it may remain asymptomatic for a few years, symptoms will usually present by early childhood. Common symptoms include hyperactivity, speech impediment, developmental delay, learning difficulties, and sometimes mental retardation.

3.9.3 Prevalence

Histidinemia is a somewhat rare disorder. However, in Japan, it is the single most prevalent inborn error of metabolism.

3.10 Maple syrup urine

3.10.1 Introduction

Maple syrup urine disease (MSUD), also called branched-chain ketoaciduria, is an autosomal recessive metabolic disorder affecting branched-chain amino acids. It is one type of organic acidemia. The condition gets its name from the distinctive sweet odor of affected infants' urine.

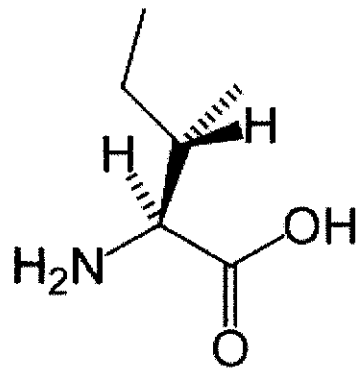


Figure 3.10.1 Structure of Iso-leucine

3.10.2 Classification

Maple syrup urine disease can be classified by its pattern of signs and symptoms, or by its genetic cause. The most common and severe form of the disease is the classic type, which appears soon after birth. Variant forms of the disorder may appear later in infancy or childhood and are typically less severe, but still involve mental and physical problems if left untreated.

There are several variations of the disease:

- Classic Severe MSUD
- Intermediate MSUD
- Intermittent MSUD

- Thiamine-responsive MSUD
- E3-Deficient MSUD with Lactic Acidosis

3.10.3 Diagnosis & Symptoms

MSUD is caused by a deficiency of the branched-chain alpha-keto acid dehydrogenase complex (BCKDH), leading to a buildup of the branched-chain amino acids (leucine, isoleucine, and valine) and their toxic by-products in the blood and urine.

The disease is characterized in an infant by the presence of sweet-smelling urine, with an odor similar to that of maple syrup. Infants with this disease seem healthy at birth but if left untreated suffer severe brain damage, and eventually die.

From early infancy, symptoms of the condition include poor feeding, vomiting, dehydration, lethargy, hypotonia, seizures, ketoacidosis, opisthotonus, pancreatitis, coma and neurological decline.

3.10.4 Management

Keeping MSUD under control requires careful monitoring of blood chemistry and involves both a special diet and frequent testing.

A diet with minimal levels of the amino acids leucine, isoleucine, and valine must be maintained in order to prevent neurological damage. As these three amino acids are required for proper metabolic function in all people, specialized protein preparations containing substitutes and adjusted levels of the amino acids have been synthesized and tested, allowing MSUD patients to meet normal nutritional requirements without causing harm.

Usually, patients are also monitored by a dietitian. Their diet must be adhered to strictly and permanently. However, with proper management those afflicted are able to live healthy, normal lives and not suffer the severe neurological damage associated with the disease.

3.10.5 Treatment

The main treatment for maple syrup urine disease is restriction of dietary forms of the three amino acids leucine, isoleucine, and valine. These restrictions must be lifelong. There are several commercial formulas and foods for individuals with MSUD.

One concern for treatment of MSUD is that when an affected individual is sick, injured, or has surgery, the disorder is exacerbated. Most individuals will require hospitalization during these times for medical management to prevent serious complications.

Fortunately, with adherence to the dietary restrictions and regular medical checkups individuals with maple syrup urine disease can live long and relatively healthy lives.

3.11 Phenylketonuria

3.11.1 Introduction

Phenylketonuria (PKU) is an inherited error of metabolism caused by a deficiency in the enzyme phenylalanine hydroxylase. Loss of this enzyme results in mental retardation, organ damage, and unusual posture and can, in cases of maternal PKU, severely compromise pregnancy. Classical PKU is an autosomal recessive disorder, caused by mutations in both alleles of the gene for phenylalanine hydroxylase (PAH), found on chromosome 12. In the body, phenylalanine hydroxylase converts the amino acid phenylalanine to tyrosine, another amino acid. Mutations in both copies of the gene for PAH mean that the enzyme is inactive or is less efficient, and the concentration of phenylalanine in the body can build up to toxic levels. In some cases, mutations in PAH will result in a phenotypically mild form of PKU called hyperphenylalanemia. Both diseases are the result of a variety of mutations in the PAH locus; in those cases where a patient is heterozygous for two mutations of PAH (ie each copy of the gene has a different mutation), the milder mutation will predominate.

The incidence of PKU is about 1 in 15,000 births, but the incidence varies widely in different human populations from 1 in 4,500 births among the population of Ireland to 1 in 13,000 births in Norway to fewer than one in 100,000 births among the population of Finland. Turkey, at 1 in 2600, has the highest incidence rate in the world. The illness is also more common in Italy and China, as well as in Yemeni populations.

3.11.2 Symptoms

- Itchy rashes
- Small head
- Shaking or jerking motions
- Seizures
- Hyperactivity (lots of energy)
- developmentally disabled
- Urine or sweat smells strange (some people think it smells like mice)
- Light coloration (pale skin, blonde hair and blue eyes)

3.11.3 Pathophysiology

Classical PKU is caused by a mutated gene for the enzyme phenylalanine hydroxylase (PAH), which converts the amino acid phenylalanine to other essential compounds in the body. Other non-PAH mutations can also cause PKU. This is an example of genetic heterogeneity.

Classical PKU

The PAH gene is located on chromosome 12 in the bands 12q22-q24.1. More than four hundred disease-causing mutations have been found in the PAH gene. PAH deficiency causes a spectrum of disorders including classic phenylketonuria (PKU) and hyperphenylalaninemia (a less severe accumulation of phenylalanine) PKU is an autosomal recessive genetic disorder, meaning that each parent must have at least one mutated allele of the gene for PAH, and the child must inherit two mutated alleles, one

from each parent. As a result, it is possible for a parent with PKU phenotype to have a child without PKU if the other parent possesses at least one functional allele of the PAH gene; but a child of two parents with PKU will always inherit two mutated alleles, and therefore the disease. Phenylketonuria can exist in mice, which have been extensively used in experiments into an effective treatment for PKU. The macaque monkey's genome was recently sequenced, and it was found that the gene encoding phenylalanine hydroxylase has the same sequence which in humans would be considered the PKU mutation.

Tetrahydrobiopterin-deficient hyperphenylalaninemia

A rarer form of hyperphenilalaninemia occurs when PAH is normal but there is a defect in the biosynthesis or recycling of the cofactor tetrahydrobiopterin (BH_4) by the patient.This cofactor is necessary for proper activity of the enzyme.Levels of dopamine can be used to distinguish between these two types. Tetrahydrobiopterin is required to convert phenylalanine to tyrosine, but it is also required to convert tyrosine to DOPA (via the enzyme tyrosine hydroxylase), which in turn is converted to dopamine. Low levels of dopamine lead to high levels of prolactin. By contrast, in classical PKU, prolactin levels would be relatively normal. Tetrahydrobiopterin deficiency can be caused by defects in four different genes. These types are known as HPABH4A, HPABH4B, HPABH4C, and HPABH4D.

3.11.4 Screening & Presentation

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. If a child is not screened during the routine Newborn Screening test (typically performed at least 12 hours and generally 24–28 hours after birth, using samples drawn by Neonatal heel prick), the disease may present clinically with seizures, albinism (excessively fair hair and skin), and a "musty odor" to the baby's sweat and urine (due to phenylacetate, one of the ketones produced).

In most cases a repeat test should be done at approximately 2 weeks of age to verify the initial test and uncover any phenylketonuria that was initially missed.

Untreated children are normal at birth, but fail to attain early developmental milestones, develop microcephaly, and demonstrate progressive impairment of cerebral function. Hyperactivity, EEG abnormalities and seizures, and severe learning disabilities are major clinical problems later in life. A "musty or mousy" odor of skin, hair, sweat and urine (due to phenylacetate accumulation); and a tendency to hypopigmentation and eczema are also observed. In contrast, affected children who are detected and treated are less likely to develop neurological problems or have seizures and mental retardation, though such clinical disorders are still possible.

3.11.5 Treatment

In the past, children with PKU almost always died from having too much phenylalanine in their bodies. Today, scientists know what foods have phenylalanine in them, and they have created a special diet for people with PKU. Since they cannot use it, people with PKU cannot eat foods that have a lot of phenylalanine, like eggs, meat and milk. An artificial sweetener called aspartame, which is used to flavour diet sodas and candies, also has a lot of phenylalanine, so people with PKU have to be careful to avoid anything with aspartame in it. People with PKU also have to take a lot of vitamins to make up for the foods they cannot eat, especially vitamins B6 and B12. Babies with PKU are fed a special formula called Lofenelac. It has everything babies need to stay healthy, but with very little phenylalanine. There are also other formulas for older children and young adults, PhenylAde and other types are available, As well as Low Protein breads and flour (Made from corn instead of regular wheat)

Women with PKU who are pregnant or trying to get pregnant have to be especially careful to follow this diet. If they do not follow the diet, their babies could be born with severe birth defects and mental retardation. Babies born to women with PKU who have followed the PKU diet throughout their pregnancy are usually healthy and do not necessarily but may develop PKU. Whether or not they have PKU themselves

depends on the mother and father's genes. As well as the Fact that Genetics may play a part, but in fact there are people who are Carriers instead of hosts (Dormant Genes) that can be passed on until they resurface in the future generations. These are so far undetectable and random at best, however it is subject to debate whether it is the mother or fathers genes that are dominant. While PKU kids are generally small in size and are usually attributed with blond hair and blue eyes, they also tend to have very fair skin (Noted only in female PKU currently) and tend to burn easily. Solar protection is a must for those who wish to work, Play, or engage in activities outdoors.

3.12 Tyrosinemia

3.12.1 Introduction

Tyrosinemia (or "Tyrosinemia") is an error of metabolism, usually inborn, in which the body cannot effectively break down the amino acid tyrosine. Symptoms include liver and kidney disturbances and mental retardation. Most inborn forms of tyrosinemia produce hypertyrosinemia (high levels of tyrosine)

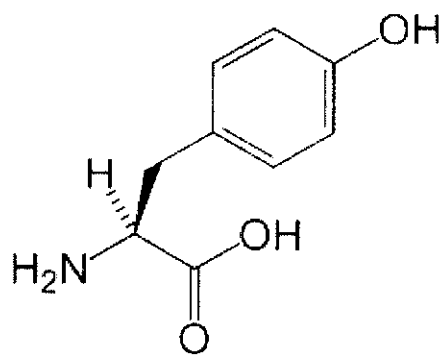


Figure 3.12.1 Structure of L-Tyrosine skeleton

3.12.2 Types

There are three types of tyrosinemia, each with distinctive symptoms and caused by the deficiency of a different enzyme.

- Type I tyrosinemia
- Type II tyrosinemia
- Type III tyrosinemia

Type I Tyrosinemia

Type I tyrosinemia is the most severe form of this disorder and is caused by a shortage of the enzyme fumarylacetoacetate hydrolase (EC 3.7.1.2), encoded by the gene FAH found on chromosome number 15. Fumarylacetoacetate hydrolase is the last in a series of five enzymes needed to break down tyrosine. Symptoms of type I tyrosinemia usually appear in the first few months of life and include failure to gain weight and grow at the expected rate (failure to thrive), diarrhea, vomiting, yellowing of the skin and whites of the eyes (jaundice), cabbage like odor, and increased tendency to bleed (particularly nosebleeds). Type I tyrosinemia can lead to liver and kidney failure, problems affecting the nervous system, and an increased risk of liver cancer.

Worldwide, type I tyrosinemia affects about 1 person in 100,000. This type of tyrosinemia is much more common in Quebec, Canada. The overall incidence in Quebec is about 1 in 16,000 individuals. In the Saguenay-Lac-Saint-Jean region of Quebec, type 1 tyrosinemia affects 1 person in 1,846.

Type II Tyrosinemia

Tyrosinemia type II (also known as "Oculocutaneous tyrosinemia," and "Richner-Hanhart syndrome") is an autosomal recessive condition with onset between ages 2 and 4 years, when painful circumscribed callosities develop on the pressure points of the palm and sole.

Pathophysiology

Type II tyrosinemia is caused by a deficiency of the enzyme tyrosine aminotransferase (EC 2.6.1.5), encoded by the gene TAT. Tyrosine aminotransferase is the first in a series of five enzymes that converts tyrosine to smaller molecules, which are excreted by the kidneys or used in reactions that produce energy. This form of the disorder can affect the eyes, skin, and mental development. Symptoms often begin in early childhood and include excessive tearing, abnormal sensitivity to light (photophobia), eye pain and redness, and painful skin lesions on the palms and soles. About half of individuals with type II tyrosinemia are also mentally retarded. Type II tyrosinemia occurs in fewer than 1 in 250,000 individuals.

Type III Tyrosinemia

Type III tyrosinemia is a rare disorder caused by a deficiency of the enzyme 4-hydroxyphenylpyruvate dioxygenase (EC 1.13.11.27), encoded by the gene HPD. This enzyme is abundant in the liver, and smaller amounts are found in the kidneys. It is one of a series of enzymes needed to break down tyrosine. Specifically, 4-hydroxyphenylpyruvate dioxygenase converts a tyrosine byproduct called 4-hydroxyphenylpyruvate to homogentisic acid. Characteristic features of type III tyrosinemia include mild mental retardation, seizures, and periodic loss of balance and coordination (intermittent ataxia). Type III tyrosinemia is very rare; only a few cases have been reported.

3.12.3 Inheritance

These disorders most often follow an autosomal recessive inheritance pattern. With recessive disorders affected patients usually have two copies of a disease gene (or mutation) in order to show symptoms. People with only one copy of the disease gene (called carriers) generally do not show signs or symptoms of the condition but can pass the disease gene to their children. When both parents are carriers of the disease gene for a particular disorder, there is a 25% chance with each pregnancy that they will have a child

affected with the disorder. As with all genetic diseases, genetic counseling may be appropriate to help families understand recurrence risks and ensure that they receive proper evaluation and care.

3.12.4 Treatment

Patients with Transient Tyrosinemia can benefit from reducing the protein level in formula and usually do well on breast milk. Normalization of the Tyrosine level is hastened by dietary supplementation with vitamin C. Patients with Type I disease must be treated aggressively with dietary restriction of Tyrosine and Phenylalanine, and administration of 2(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC). This drug inhibits 4HPPD and lowers Tyrosine metabolites that are responsible for much of the Type I morbidity. Liver transplantation is a cure for patients with Type I disease, providing normal FAH activity. Patients with Type II Tyrosinemia also require dietary restriction of Tyrosine and Phenylalanine, respond to vitamin A supplementation in clearing of the skin lesions and should be given a trial of pyridoxine phosphate. Patients with Type III benefit from dietary Tyrosine and Phenylalanine restriction.

Because the diagnosis and therapy of Tyrosinemia is complex, the pediatrician is advised to manage the patient in close collaboration with a consulting pediatric metabolic disease specialist. It is recommended that parents travel with a letter of treatment guidelines from the patient`s physician.

Chapter-IV

Materials and Methods

4. MATERIALS AND METHODS

Database is the easiest and convenient way to storing and retrieving information. Aminoacid Disorders data has been expanding exponentially over the years. Hence, there is an urgent need for properly arranging the data to meet specific needs to make the data available to public to facilitate advance research in corresponding fields.

Information about Amino acid Disorder is scattered along various literature, thus the information were collected from published literature from various sources such as OMIM, Entrez, EMBL, UNIGENE, ENSEMBL, UNIPROT, REF SEQ, INTERPRO, PFAM, and PRODOM and from various publications.

Amino acids are the building blocks of proteins and have many functions in the body. Hereditary disorders of amino acid processing can result from defects either in the breakdown of amino acids or in the body's ability to get amino acids into cells. Because these disorders cause symptoms early in life, newborns are routinely screened for several common ones. In the United States, newborns are commonly screened for phenylketonuria, maple syrup urine disease, homocystinuria, tyrosinemia, and a number of other inherited disorders, although screening varies from state to state. Everyone with one of these inherited metabolic disorders must have a specific diet, planned in accordance their metabolic tolerance. The diet must be supervised by a qualified nutritionist or physician knowledgeable about the condition, and must be monitored regularly through blood tests.

4.1 **OMIM** (Online Mendelian Inheritance in Man)

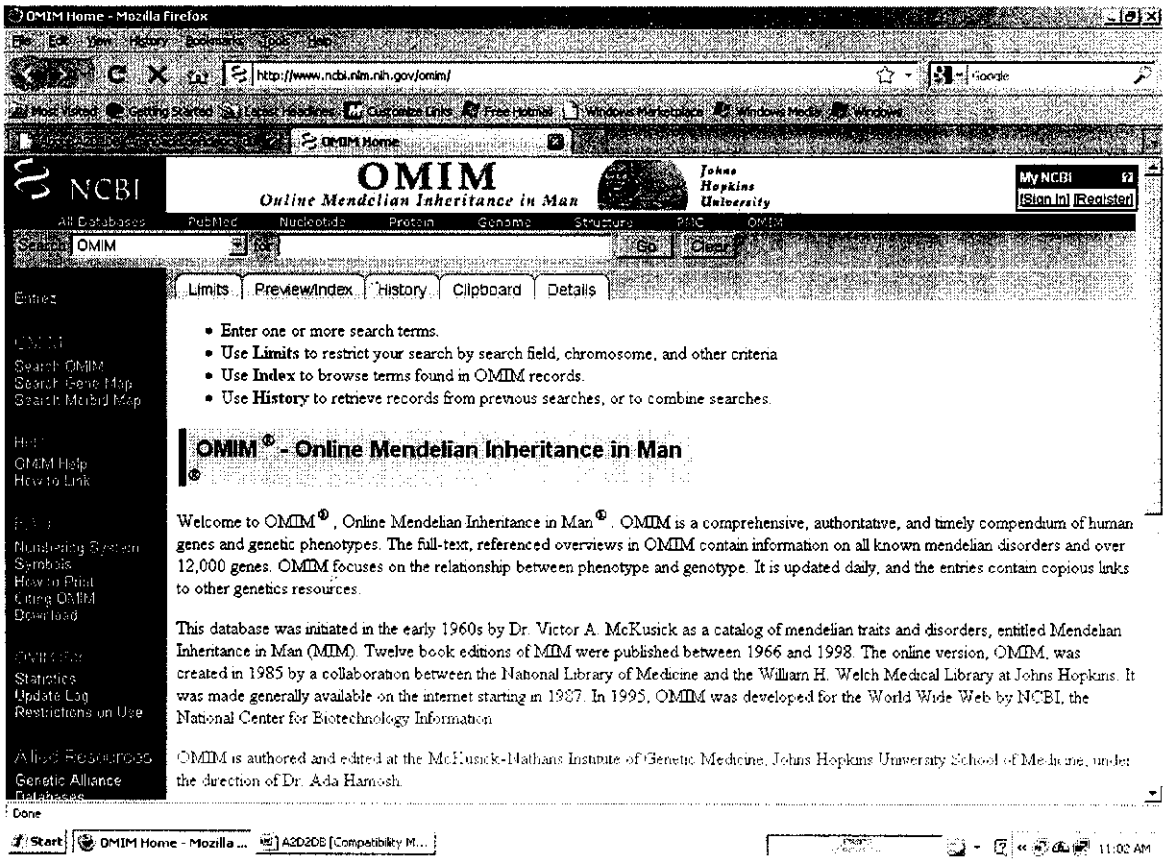


Figure 4.1 OMIM

This database was initiated in the early 1960s by Dr. Victor A. McKusick as a catalog of Mendelian traits and disorders, entitled Mendelian Inheritance in Man (MIM). Twelve book editions of MIM were published between 1966 and 1998. The online version, OMIM, was created in 1985 by collaboration between the National Library of Medicine and the William H. Welch Medical Library at Johns Hopkins. It was made generally available on the internet starting in 1987. In 1995, OMIM was developed for the World Wide Web by NCBI, the National Center for Biotechnology Information. OMIM is authored and edited at the McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, under the direction of Dr. Ada Hamosh.

4.2 Entrez Database

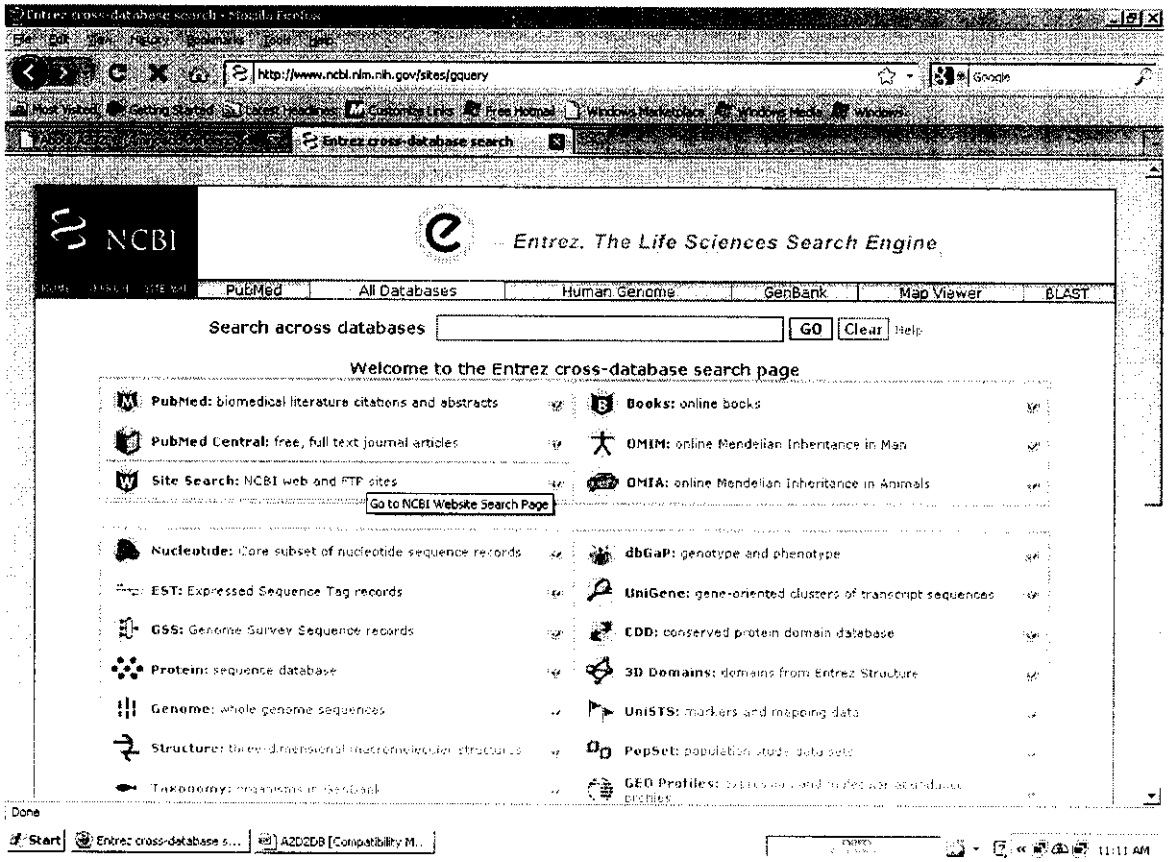


Figure 4.2 Entrez

The Entrez Global Query Cross-Database Search System is a powerful federated search engine, or web portal that allows users to search many discrete health sciences databases at the National Center for Biotechnology Information (NCBI) website. NCBI is part of the National Library of Medicine (NLM), itself a department of the National Institutes of Health (NIH) of the United States. Entrez also happens to be the French second person plural (or formal) form of the verb "to enter", meaning literally "come in".Entrez Global Query is an integrated search and retrieval system that provides access to all databases simultaneously with a single query string and user interface. Entrez can efficiently retrieve related sequences, structures, and references. The Entrez system can provide views of gene and protein sequences and chromosome maps.

4.3 EMBL Nucleotide Database

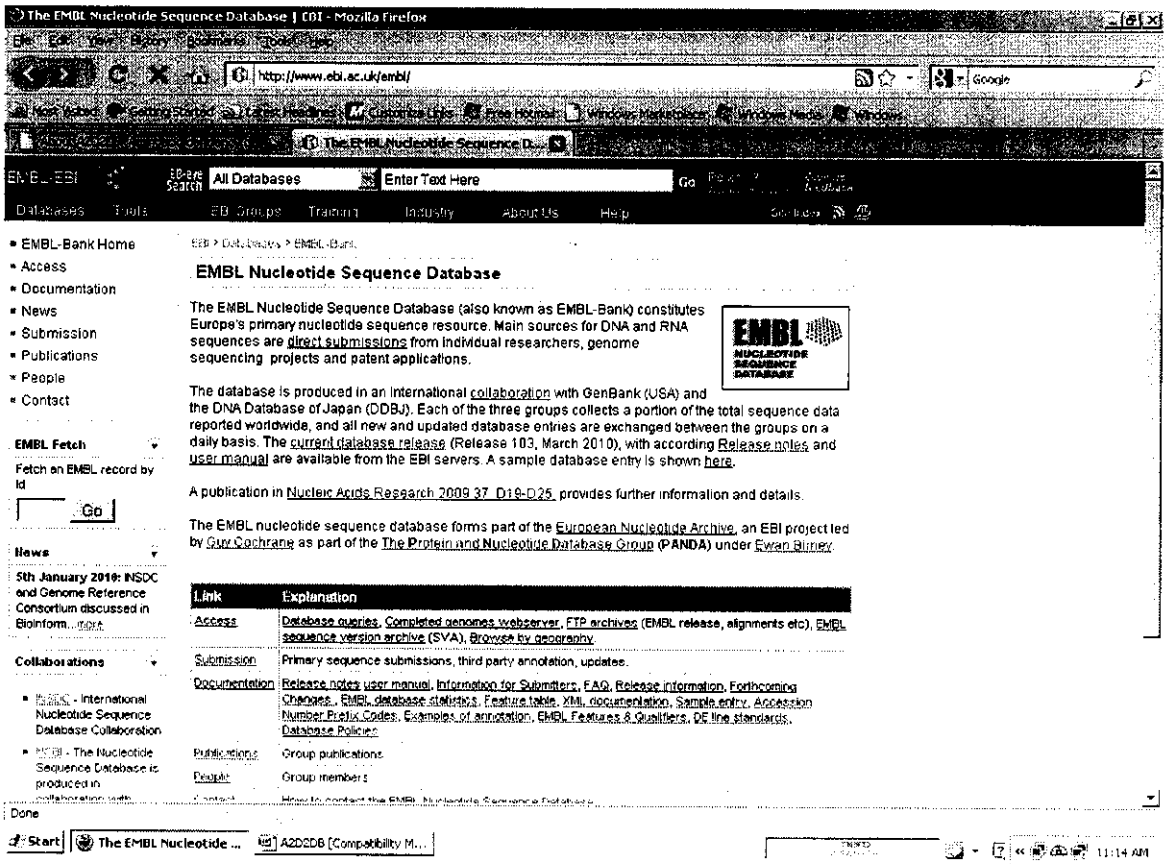


Figure 4.3 EMBL

The European Molecular Biology Laboratory (EMBL) is a molecular biology research institution supported by 20 European countries and Australia as associate member state. The EMBL was created in 1974 and is a non-profit organization funded by public research money from its member states. Research at EMBL is conducted by approximately 85 independent groups covering the spectrum of molecular biology. The Laboratory operates from five sites: the main Laboratory in Heidelberg, and Outstations in Hinxton (the European Bioinformatics Institute (EBI)), Grenoble, Hamburg, and Monterotondo near Rome. Each of the sites has a research specific field. At EBI, the research is oriented towards computational biology and bioinformatics, at Grenoble and Hamburg the research is in the field of structural biology, at Monterotondo the research is

using mainly mouse models for medical related problems and last but not least in Heidelberg, the headquarters, there are big departments in cell biology and gene expression as well as smaller complementing the aforementioned research fields.

4.4 UniGene Database

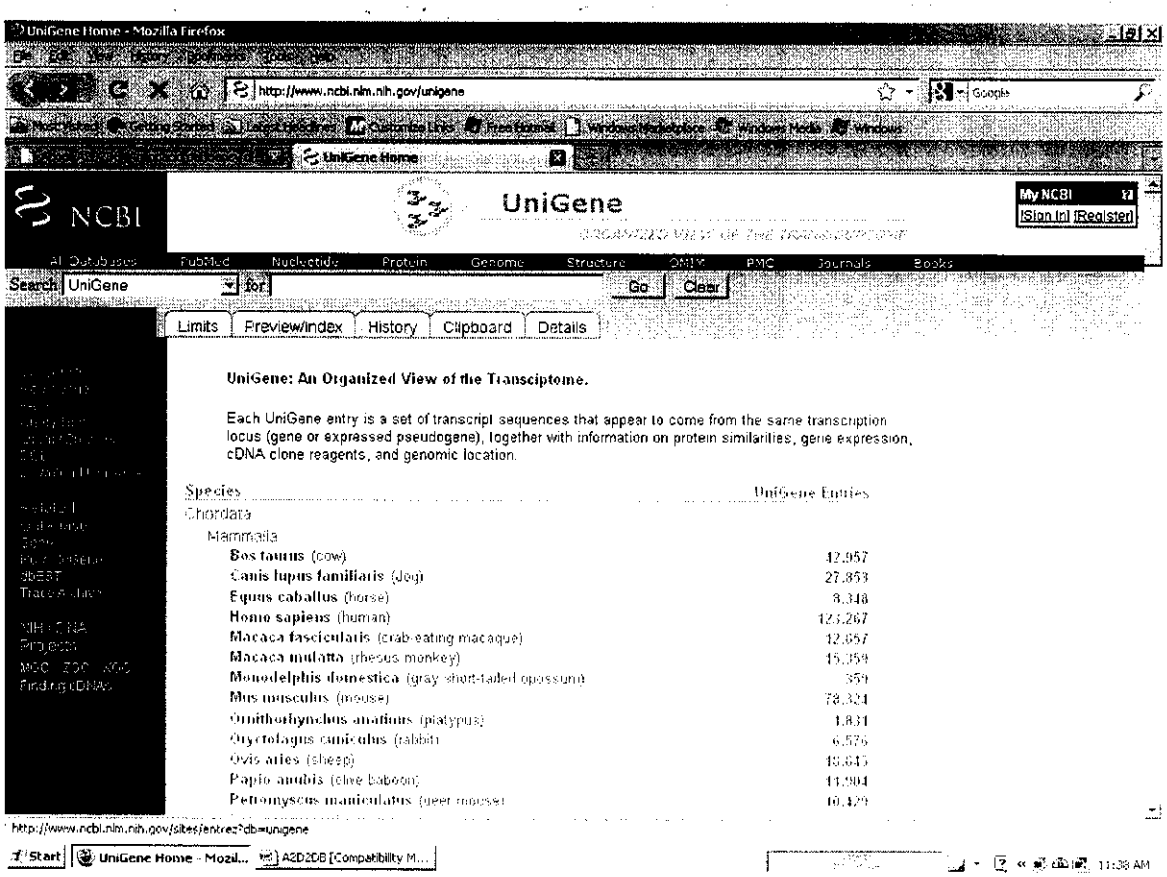


Figure 4.4 Unigene

UniGene is an NCBI database of the transcriptome and thus, despite the name, not primarily a database for genes. Each entry is a set of transcripts that appear to stem from the same transcription locus (i.e. gene or expressed pseudogene). Information on protein similarities, gene expression, and cDNA clones, and genomic location is included with each entry.

4.5 ENSEMBL Database

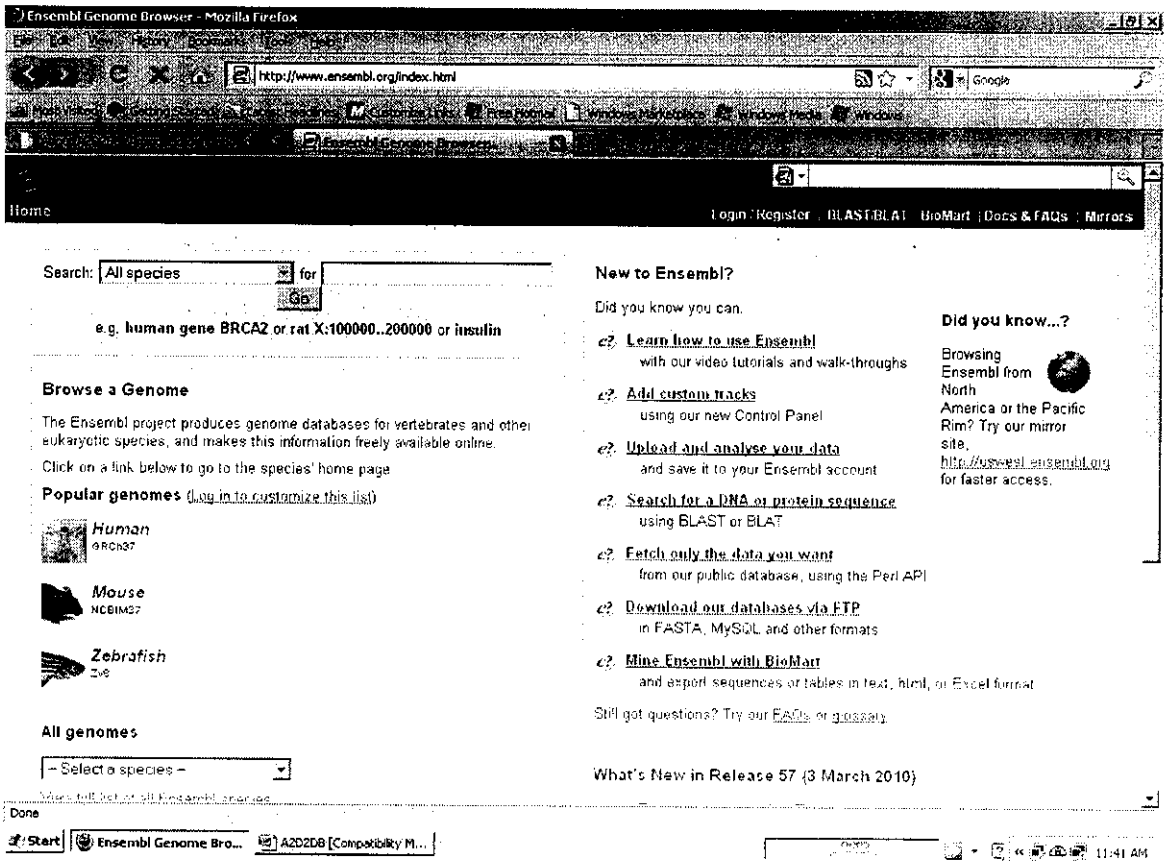


Figure 4.5 ENSEMBL

Ensembl is a joint scientific project between the European Bioinformatics Institute and the Wellcome Trust Sanger Institute, which was launched in 1999 in response to the imminent completion of the Human Genome Project with scientists in the United States, the international consortium comprised geneticists in China, France, Germany, and the United Kingdom. Its aim is to provide a centralised resource for geneticists, molecular biologists and other researchers studying the genomes of our own species and other vertebrates. Ensembl is one of several locations for the retrieval of genomic information. Similar databases and browsers are found at NCBI and the University of California, Santa Cruz (UCSC)

4.6 Uniprot Database

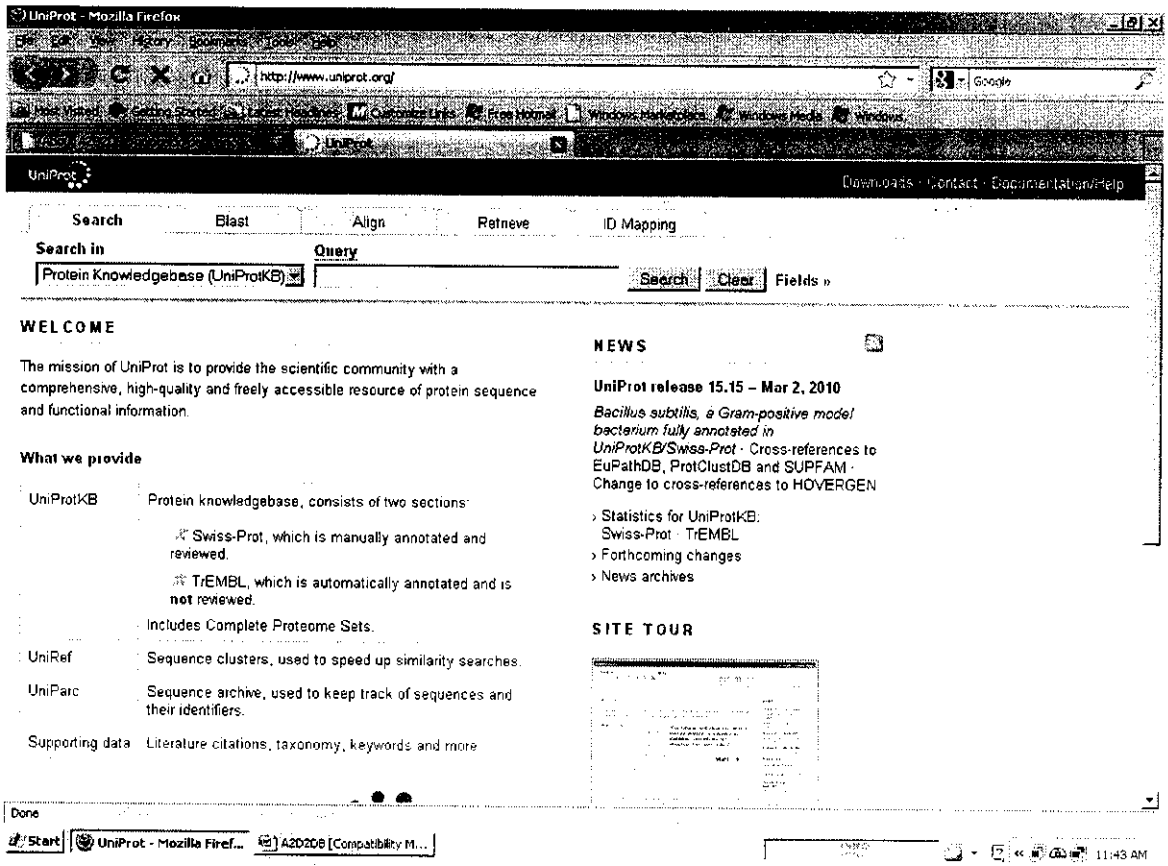


Figure 4.6 Uniprot

UniProt is the universal protein resource, a central repository of protein data created by combining Swiss-Prot, TrEMBL and PIR. This makes it the world's most comprehensive resource on protein information. The UniProt Consortium comprises the European Bioinformatics Institute (EBI), the Swiss Institute of Bioinformatics (SIB), and the Protein Information Resource (PIR). EBI located at the Wellcome Trust Genome Campus in Hinxton, UK, hosts a large resource of bioinformatics databases and services. SIB, located in Geneva, Switzerland, maintains the ExPASy (Expert Protein Analysis System) servers that are a central resource for proteomics tools and databases. PIR, hosted by the National Biomedical Research Foundation (NBRF) at the Georgetown University Medical Center in Washington, DC, USA, is heir to the oldest protein

sequence database, Margaret Dayhoff's Atlas of Protein Sequence and Structure. In 2002, EBI, SIB, and PIR joined forces as the UniProt Consortium.

4.7 Ref Seq Database

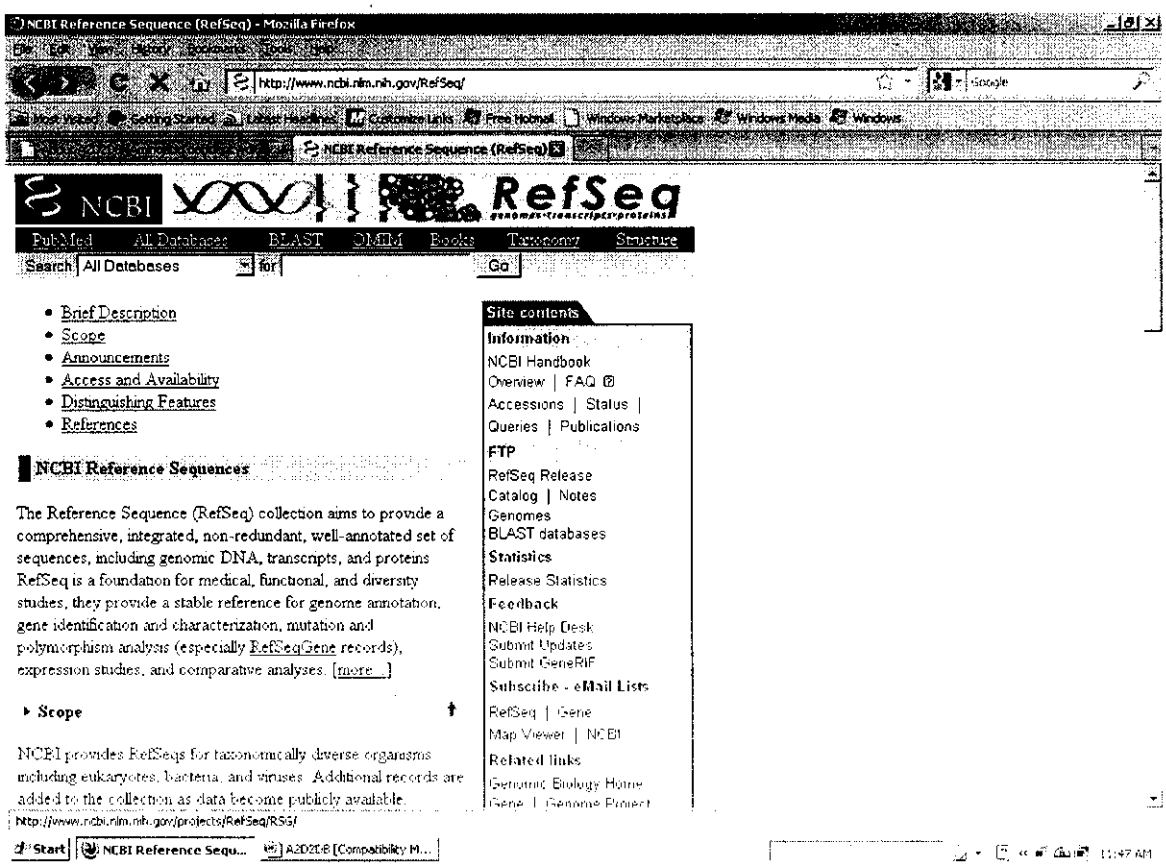


Figure 4.7 Ref Seq

The Reference Sequence (RefSeq) database is an open access, annotated and curated collection of publicly available nucleotide sequences (DNA, RNA) and their protein translations. This database is built by National Center for Biotechnology Information (NCBI), and, unlike GenBank, provides only one example of each natural biological molecule for major organisms ranging from viruses to bacteria to eukaryotes.

For each model organism, RefSeq aims to provide separate and linked records for the genomic DNA, the gene transcripts, and the proteins arising from those transcripts.

RefSeq is limited to major organisms for which sufficient data is available (more than 8,000 distinct "named" organisms as of April 2009), while GenBank includes sequences for any organism submitted (approximately 250,000 different named organisms).

4.8 Interpro database

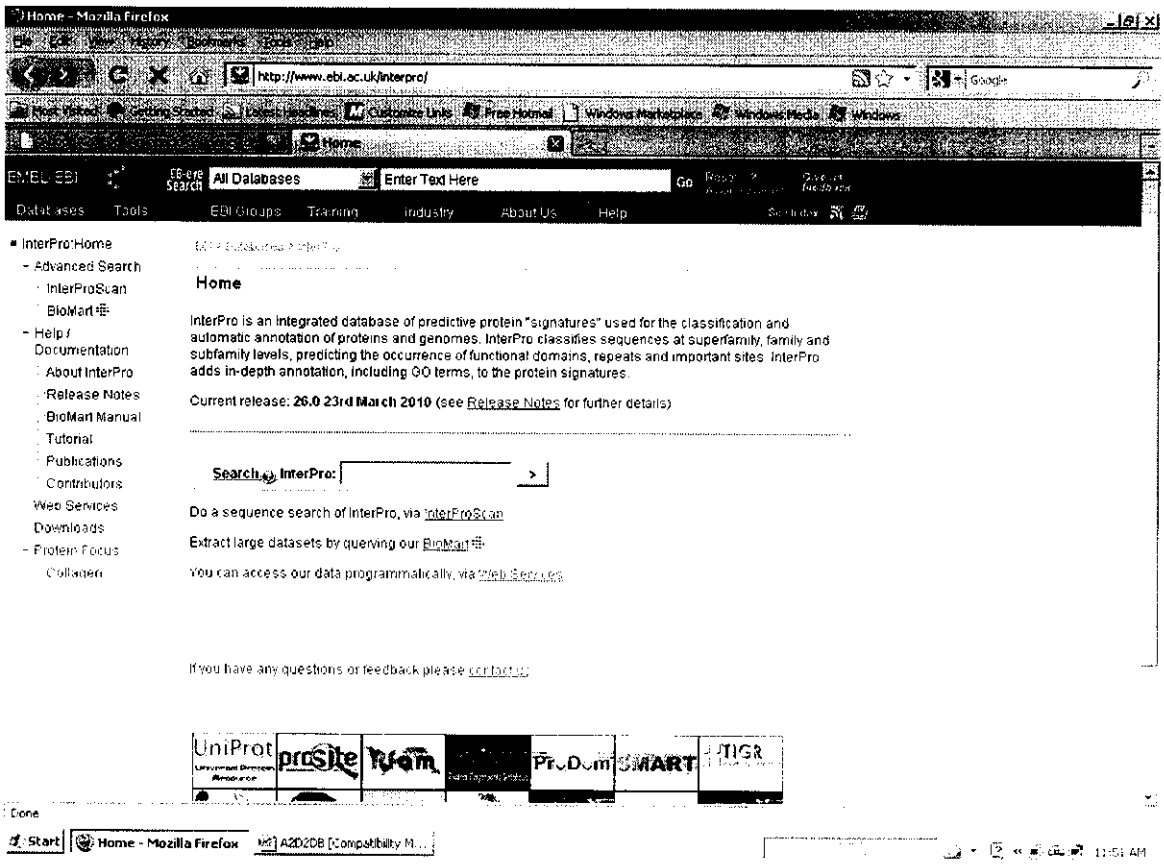


Figure 4.8 Interpro

InterPro is a database of protein families, domains and functional sites in which identifiable features found in known proteins can be applied to new protein sequences.

The contents of InterPro are based around diagnostic signatures and the proteins that they significantly match. The signatures consist of models (simple types, such as regular expressions or more complex ones, such as Hidden Markov models) which describe protein families, domains or sites. Models are built from the amino acid sequences of

known families or domains and they are subsequently used to search unknown sequences (such as those arising from novel genome sequencing) in order to classify them. Each of the member databases of InterPro contribute towards a different niche, from very high-level, structure-based classifications (SUPERFAMILY and CATH-Gene3D) through to quite specific sub-family classifications (PRINTS and PANTHER).

4.9 Pfam Database

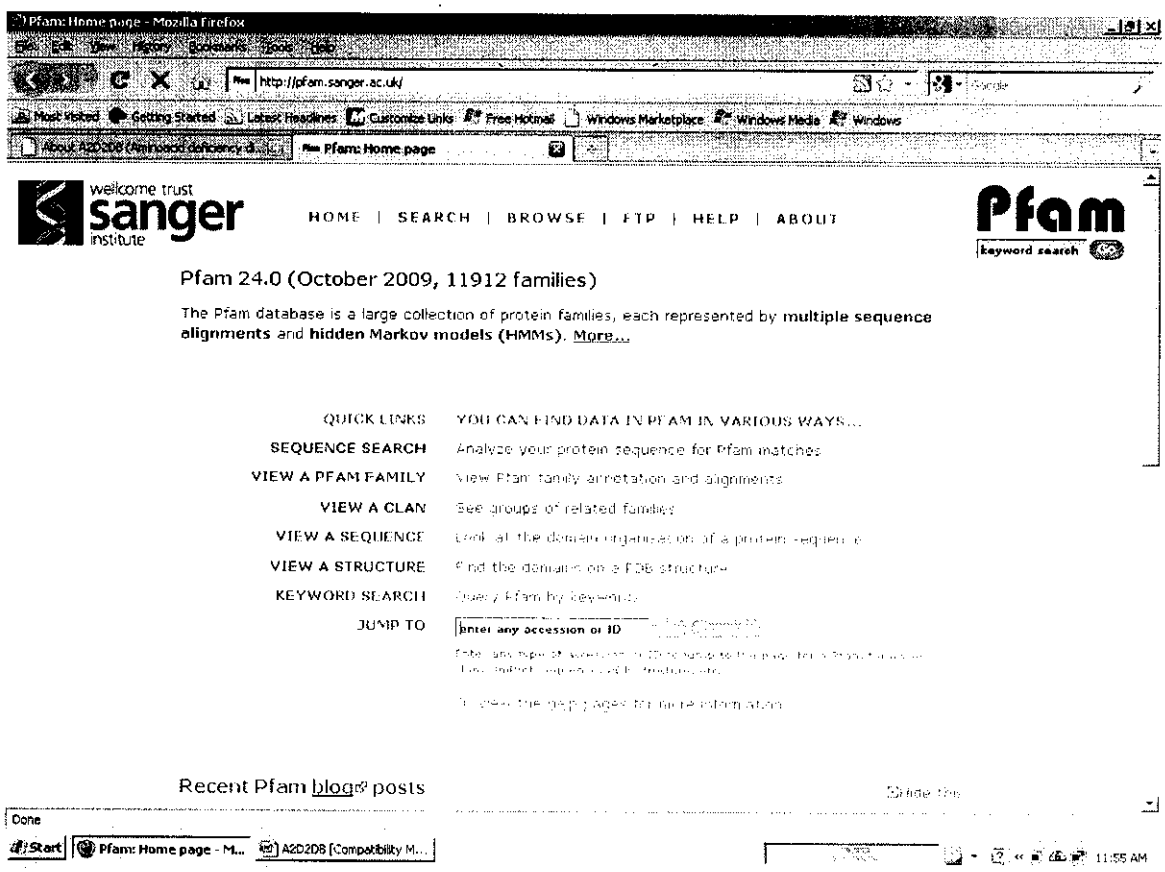


Figure 4.9 Pfam

The Pfam database contains information about protein domains and families. Pfam-A is the manually curated portion of the database that contains over 10,000 entries. For each entry a protein sequence alignment and a hidden Markov model is stored. These hidden Markov models can be used to search sequence databases with the HMMER package written by Sean Eddy. Because the entries in Pfam-A do not cover all known

proteins, an automatically generated supplement is provided called Pfam-B. Pfam-B contains a large number of small families derived from clusters produce by an algorithm called ADDA. Although of lower quality, Pfam-B families can be useful when no Pfam-A families are found.

4.10 ProDom Database

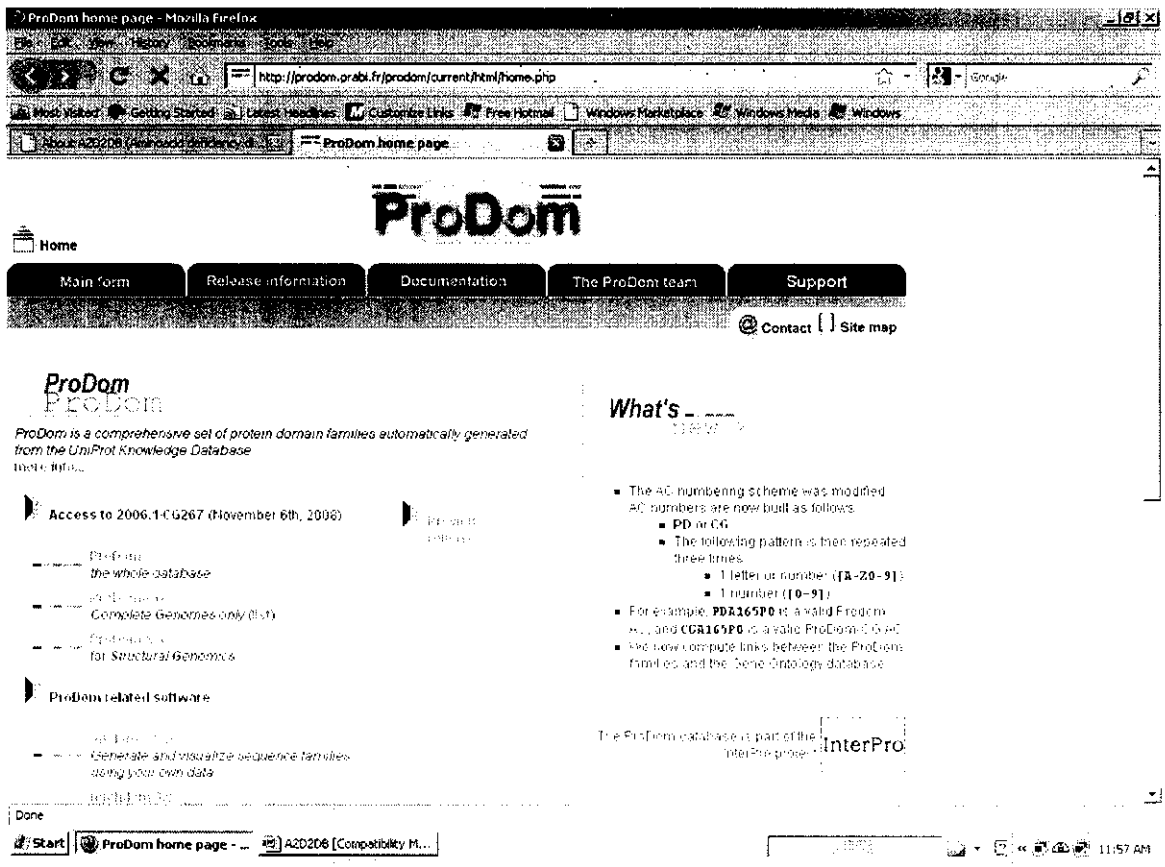


Figure 4.10 ProDom

ProDom is a database of protein families that includes their annotations and multiple sequence alignments generated using hidden Markov models.

4.11 Tools and Software's used for A^2D^2DB

- WampServer
  - ⇒ Apache
  - ⇒ PHP
  - ⇒ MySQL
- HTML
- HTML KIT
- Microsoft front page

4.11.1Wampserver

WampServer is a Windows web development environment. It allows user to create web applications with Apache, PHP and the MySQL database. WampServer is packages of independently created programs installed on computers that use a Microsoft Windows operating system. The interaction of these programs enables dynamic web pages to be served over a computer network, such as the internet or a private network.

"WAMP" is an acronym formed from the initials of the operating system (Windows) and the package's principal components: Apache, MySQL and PHP. Other programs may also be included in a package, such as phpMyAdmin which provides a graphical interface for the MySQL database manager, or the alternative scripting languages Python or Perl.

WampServer is used in this Database. MySQL is used to store 10 Aminoacid Disorders. PHP used as front end to retrieve all information from various tables of the database.

4.11.2 Apache

Apache is the Open source Web server. There are several different flavors of open source development, apache notable for playing a key role in the initial growth of the World Wide Web. Apache was the first viable alternative to the Netscape Communications Corporation web server. The majority of all web servers using Apache

are Linux web servers. The application is available for a wide variety of operating systems, including UNIX, FreeBSD, Linux, Solaris, Novell NetWare, Mac OS X, Microsoft Windows, OS/2, TPF and eComStation.

4.11.3 PHP

PHP is a powerful server side scripting language for creating dynamic and interactive websites. PHP is a widely-used general-purpose scripting language that is especially suited for Web development and can be embedded into HTML.

PHP often used together with Apache (web server on various operating systems. It also supports various databases such as MySQL, SQL, Oracle, Sybase, Informix, Generic ODBC, PostgreSQL, etc

4.11.4 MySQL

MySQL database is the world's most popular open source database because of its fast performance, high reliability, ease of use and dramatic cost savings. It is a relational database management system (RDBMS) which has more than 11 million installations. The program runs as a server providing multi-user access to a number of databases.

Some feature of the MySQL database includes

- Handles large databases, in the area of 50,000,000+records.
- No memory leaks & it strongly support windows, Linux, UNIX and Solaris.
- Tested with a commercial memory leakage detector (purify).
- A privilege and password system is very flexible, secure and allows host based verification.
- Passwords all secure since all password traffic when connecting to a server is encrypted.

4.11.5. HTML

HTML (Hypertext Markup Language) is the predominant markup language for Web pages. It provides a means to describe the structure of text-based information in a document by denoting certain text as links, headings, paragraphs, lists and so on and to supplement that text with interactive forms, embedded images and other objects. HTML is written in the form of tags, surrounded by angle brackets. HTML can also describe, to some degree, the appearance and semantics of a document and can include embedded scripting language code (such as JavaScript) which can affect the behavior of Web browsers and other HTML processors.HTML used in A^2D^2DB to create data entry form. Database designer can enter, update, modify and delete the record of the disorders.

4.11.6. HTML Kit

HTML Kit is a full-featured free editor for HTML, XHTML, XML, CSS, JavaScript, PHP and other text files. 400+ plugins are available for it, including HTML Tidy for creating standards-compliant web pages. In A^2D^2DB HTML KIT is used as the editor for HTML and PHP programs.

4.12 How A^2D^2DB Works?

User selected data in the form passes along with the URL to web server. The web server stores the user entries in variables and retrieves the requested PHP file and takes a look at it and it passes a request to the PHP 'engine' to execute them. PHP runs through the sequence of instructions in the php file. Retrieve information from the variables stored into MySQL database (Aminoacid Deficiency Disorder Database) by the web server .The PHP engine will then make a request of the Relational Database Management System (RDBMS), PHP fetch the results from MySQL Database in the form of a query written in SQL. The PHP engine completes execution of the instructions of browser query, combines all the information it's gathered and returns it all formatted as HTML to the web server. The web server then supplies the HTML page back to the requesting browser.

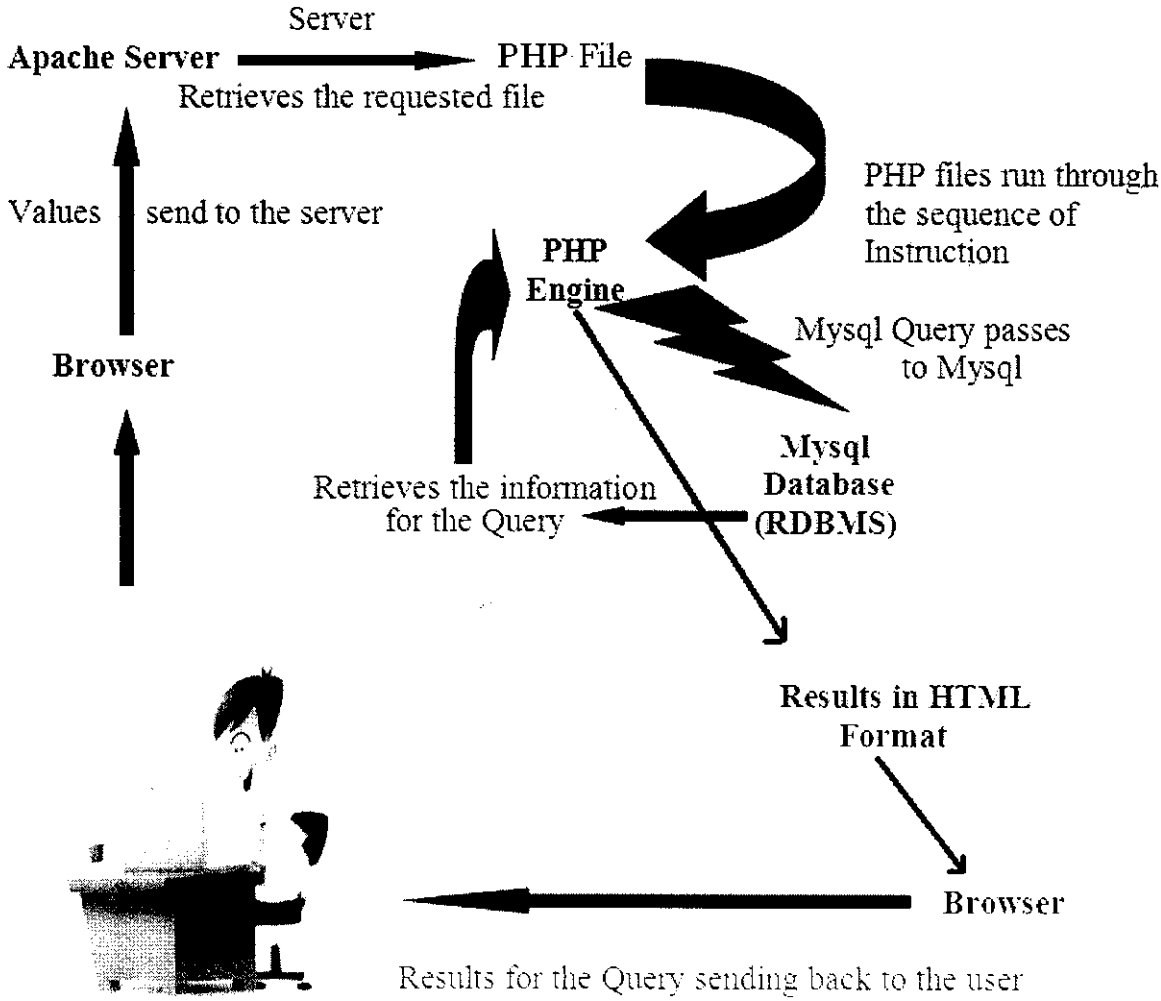

Server
Apache Server
PHP File
Retrieves the requested file
PHP files run through the sequence of Instruction
Values
send to the server
PHP Engine
Mysql Query passes to Mysql
Browser
Mysql Database (RDBMS)
Retrieves the information for the Query
Results in HTML Format
Browser
Results for the Query sending back to the user

Figure 4.12

Chapter-V

Results and Discussion

5. RESULTS AND DISCUSSION

5.1 Disorders List

Current study includes the information about the important protein metabolic disorders. Thus, a total of 10 Disorders includes Albinism, Alkaptonuria, Cystinuria, Cystinosis, Glycinuria, Hartnup's Disease, Histidinemia, Maple syrup urine disease, Phenylketonuria & Tyrosinemia were catalogued from various published literature.

5.2 Implementation of A^2D^2DB

A^2D^2DB comprises of information about the 10 important protein metabolic disorders and its individual information includes about the diseases, causes, signs & symptoms, prevalence, pathophysiology, treatment and protein details of the particular disease from PROTEIN database such as the SWISSPROT .This database was created in the Mysql and it has 15 tables that were stored and update database information.

User can get the information from database in two ways. 1. Browse by disease type, 2.Search by disease. They can select disease name in search box then can get information about result page will provide disease information of its protein from the SWISSPROT and has link with various Mysql tables such as Albinism, Alkaptonuria, Cystinuria, Cystinosis, Glycinuria, Hartnup's Disease, Histidinemia, Maple syrup urine disease, Phenylketonuria & Tyrosinemia and has link with OMIM, Entrez, EMBL, UNIGENE, ENSEMBL, UNIPROT, REF SEQ, INTERPRO, PFAM and PRODOM database.

User can get all the table information by clicking the Hyperlink, a special feature of this database is link to OMIM, Entrez, EMBL, UNIGENE, ENSEMBL,UNIPROT, REF SEQ, INTERPRO, PFAM and PRODOM database this link directly retrieve information for the particular disease from those database

5.3 Home Page of A^2D^2DB

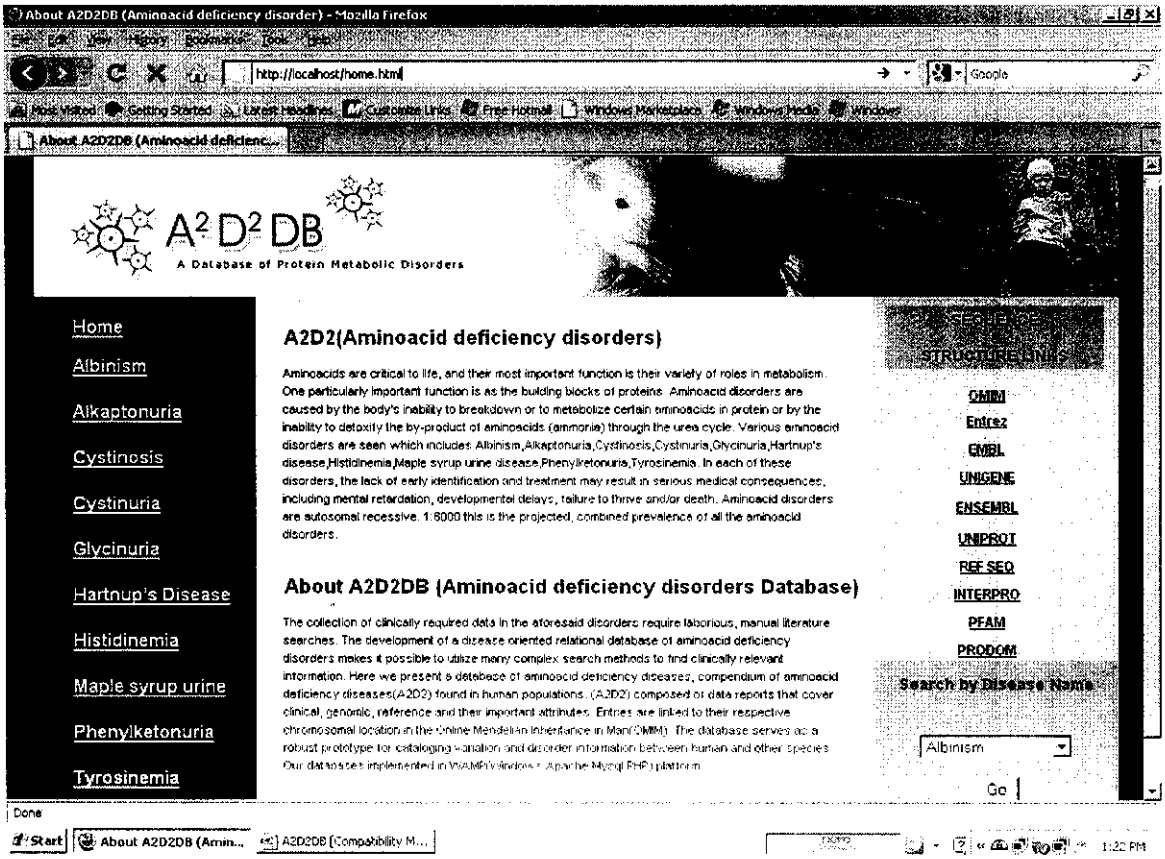


Figure 5.3 Search form of A^2D^2DB

The Home page of the Amino acid deficiency disorder database (A^2D^2DB) shows about the brief introduction of the amino acid deficiencies and also about the metabolic disorders in the left side of the page where on the right side, hyperlinks of sequence and structural links are provided to get the chromosomal level of the diseases and other important information from the online databases directly. This is a user friendly database for all the peoples and scientists to retrieve the information and to know about the protein metabolic diseases. The search by disease name tab is provided, by a single click, it is ease to retrieve the information about the individual diseases from the **SWISSPROT** database. It includes gene name, taxonomic identifier, functions, post translational modifications and other important information's of it.

In the present study, A^2D^2DB was developed with available disease level data. It is a user friendly database having interactive link to various sites. Updating of A^2D^2DB will be a continuous process as new data is made available and its discoveries. This requires the management structure that is sustainable in long term rather than project by project management. Identification guides are not only important as resource, but also because they enable many more scientists to begin to recognize previously little known metabolic disorders. Without an absolute record of the metabolic disorders, it is difficult for people to know if the diseases they look at have already been described. So database information should have complete record.

At early Michals and Matalon (1985) had created the database for the metabolic disorder phenylketonuria alone. The creation of database for the amino acid deficiency disorder is a new and innovate one of putting all protein metabolic disorders in a single site to give all the information about the above said disorders, and by visiting the side any one can know about the diseases and its importance. It is necessary to upload the current and scientific information to all the diseases to the database.

All the information's stored in the databases were retrieved from the various open sources medical and scientific websites. The disease albinism related data's are obtained from http://www.medhelp.org. It gives the important properties of the disease such as the pathophysiology, classification, inheritance etc..,

http://www.health-care-guide.org is an online official health care organization site where the data's in that site are more useful and gives the latest and updated information about the disease. The data's for the disease alkaptonuria and phenylketonuria are retrieved from this site.

http://www.news-medical.net is the literature based site that contains all the latest and research oriented data's about the metabolic disorders. This gives the information about the particular of the diseases among the people all over the world. The disease's such as the cystinuria and cystinosis based data's are uploaded from this medical site.

Creation of amino acid deficiency disorder database includes the information of the disease types and its important properties from various online resources where the data's are scattered in the net. Collecting and organizing the data's in the right format is vital and versatile for the people's to know about the disorder and to get aware of those diseases.

http://en.wikipedia.org/wiki/metabolic disorders are the general search engine site, where the information about the metabolic disorders are available widely and can be easily obtained from it. In our database all the introductory parts and the structures of the enzymes are collected from this online resource only.

http://www.medic8.com is another medical online database. It includes the various types of data's. This database is maintained by research scientist in the European countries. These databases are updated in the daily basis and the information obtained are uploaded to it to access easily.

http://www.umm.edu/article is the science and online disease database maintained by the scientist of United States. This database helped us to know the prevalence of the disease affected peoples all over the world. With the available data's in the online resources the database was created and it is ease to access if it is hosted online.

5.3.1 Albinism

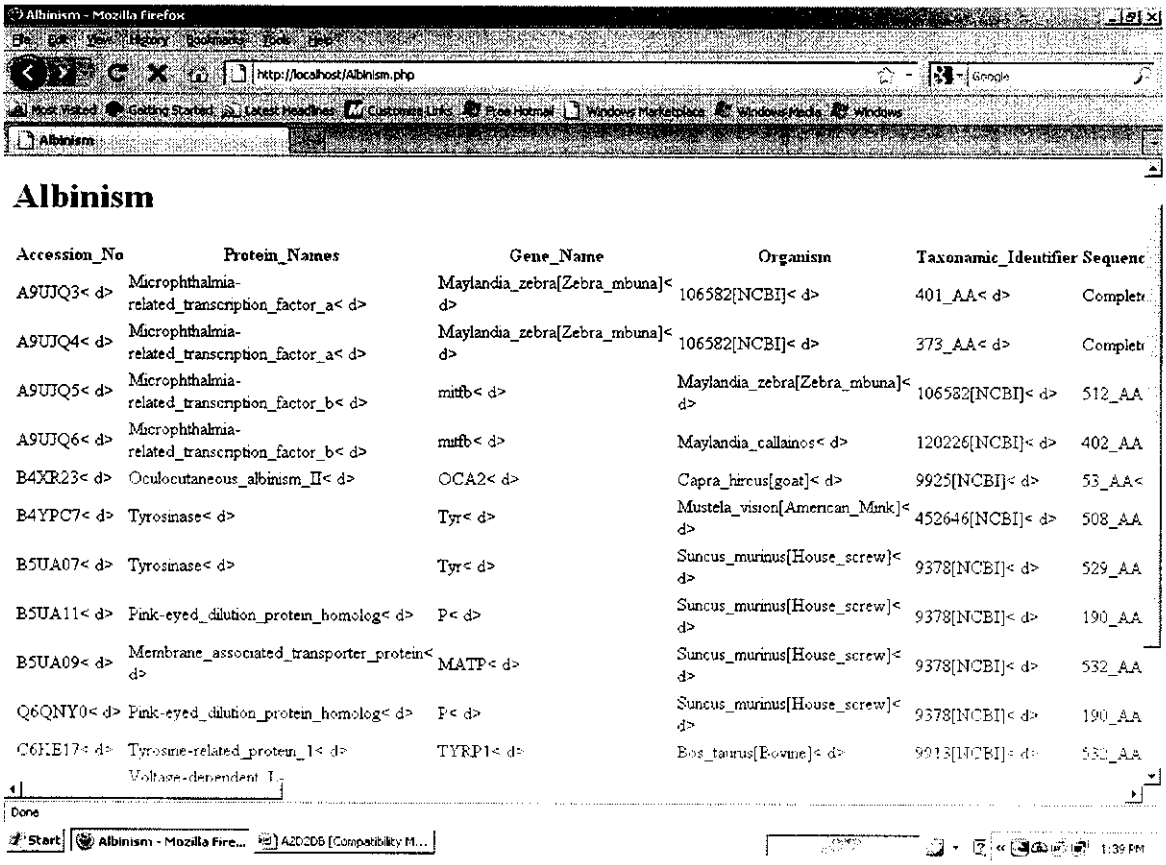


Figure 5.3.1 Information from Albinism

5.3.2 Alkaptouria

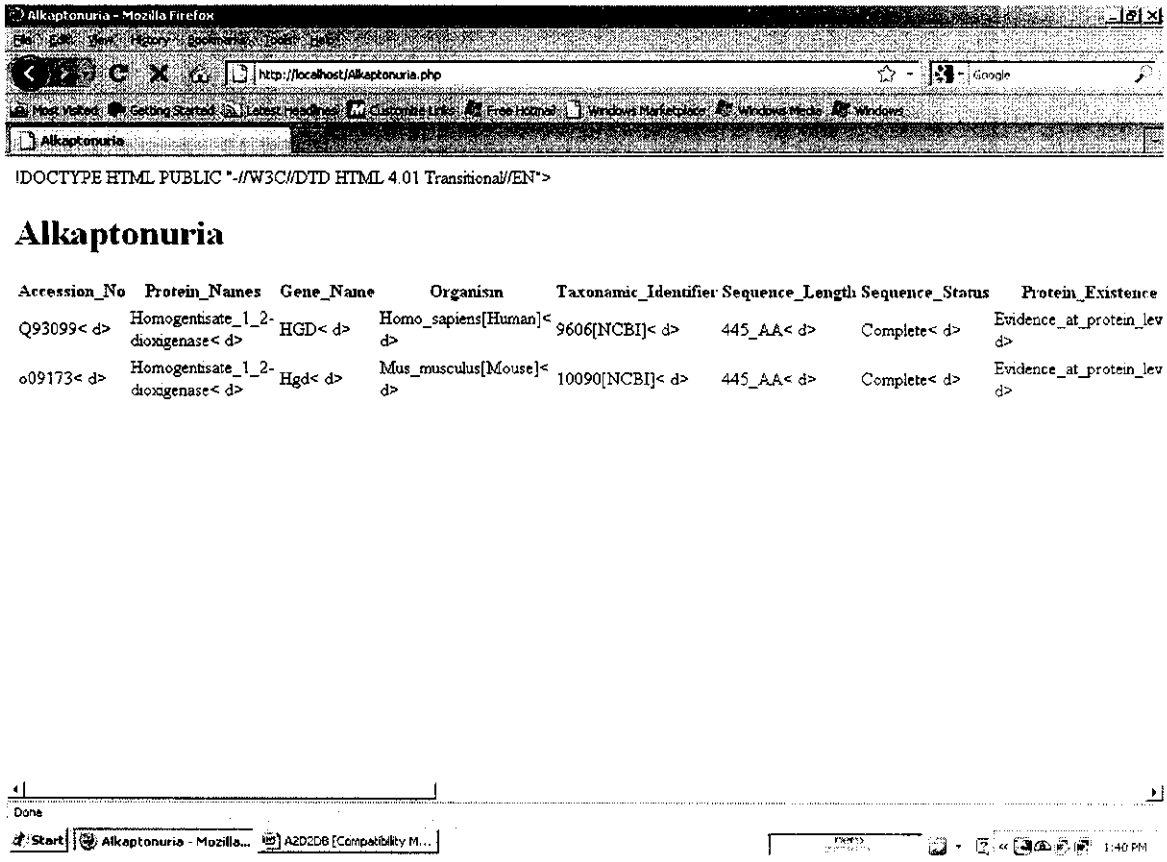


Figure 5.3.2 Information from Alkaptonuria

5.3.3 Cystinosis

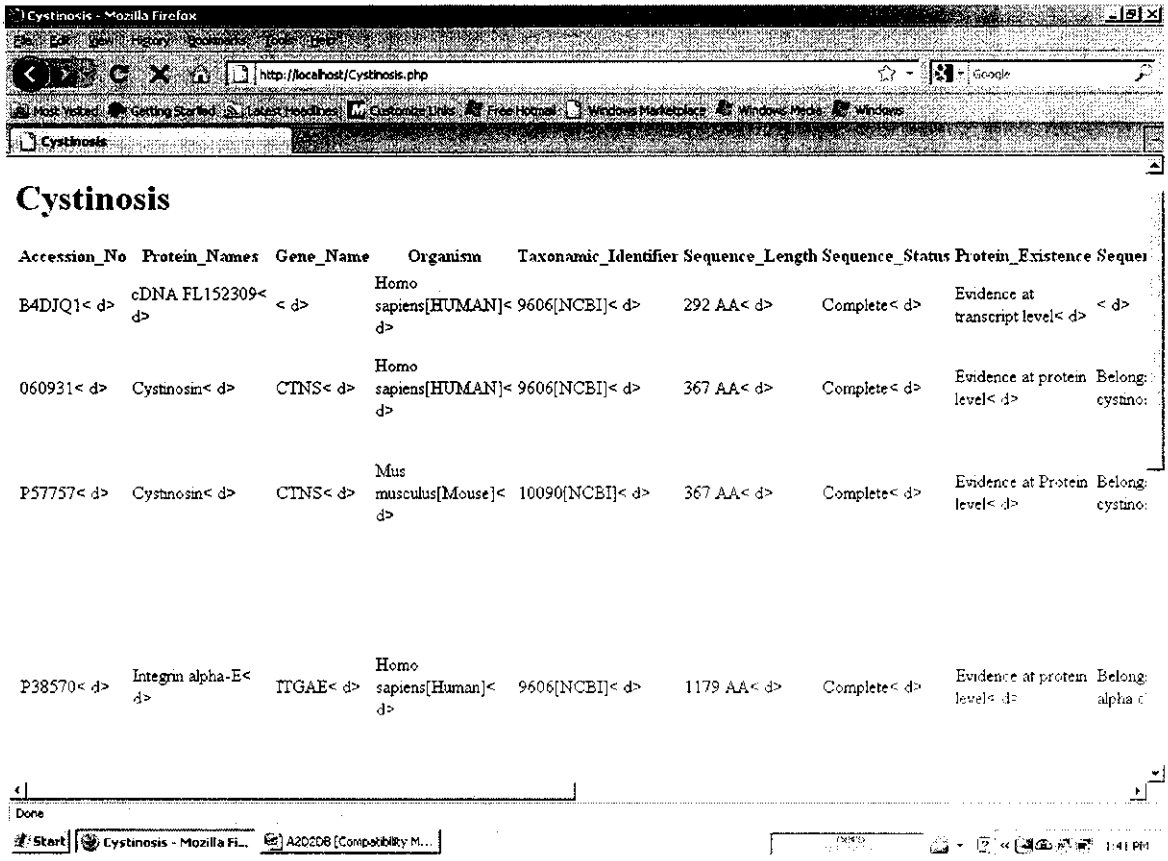


Figure 5.3.3 Information from Cystinosis

5.3.4 Cystinuria

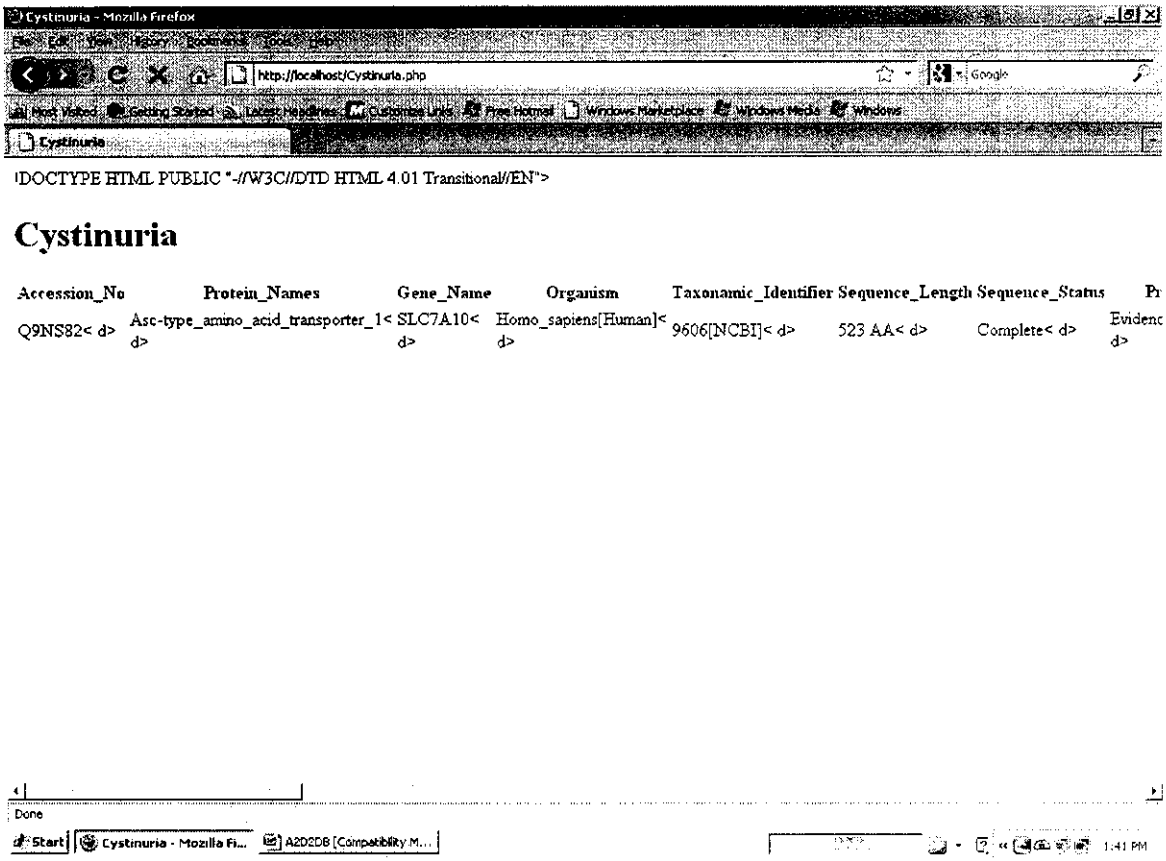


Figure 5.3.4 Information from Cystinuria

5.3.5 Glycinuria

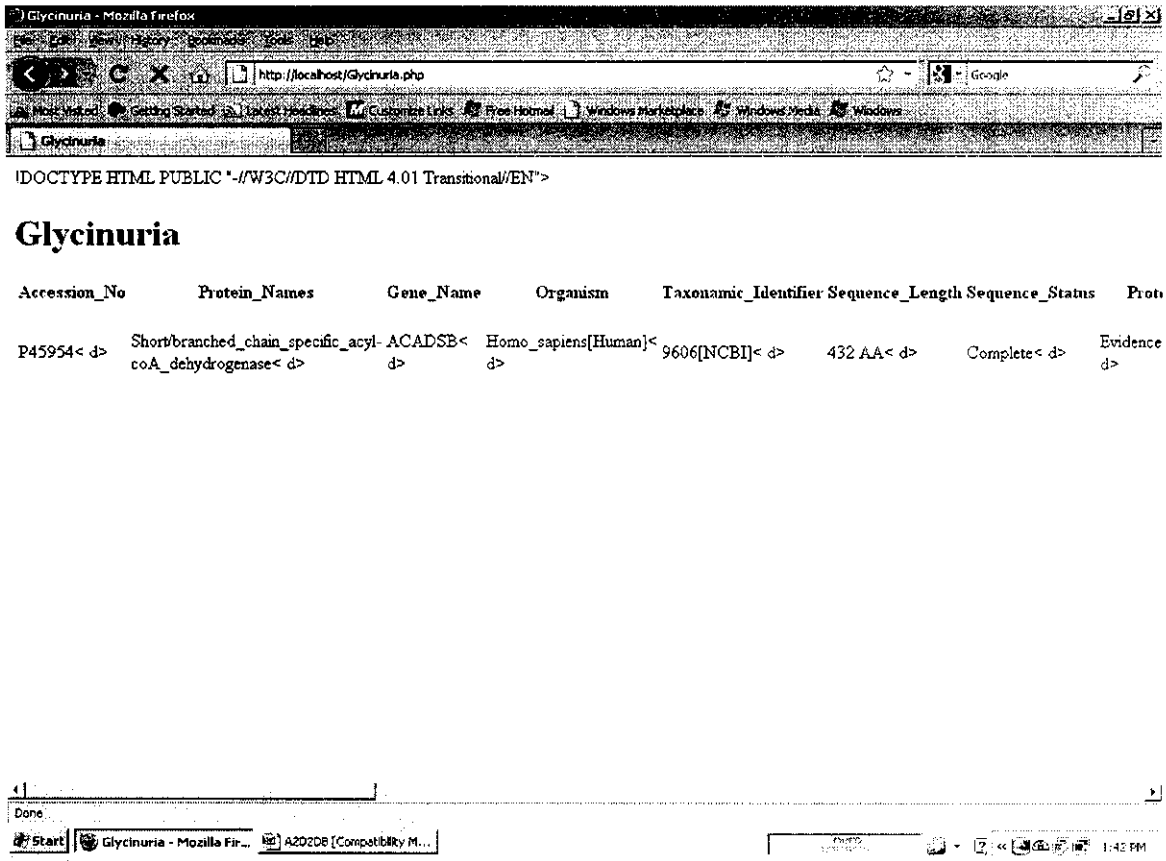


Figure 5.3.5 Information from Glycinuria

5.3.6 Hartnup's Disease

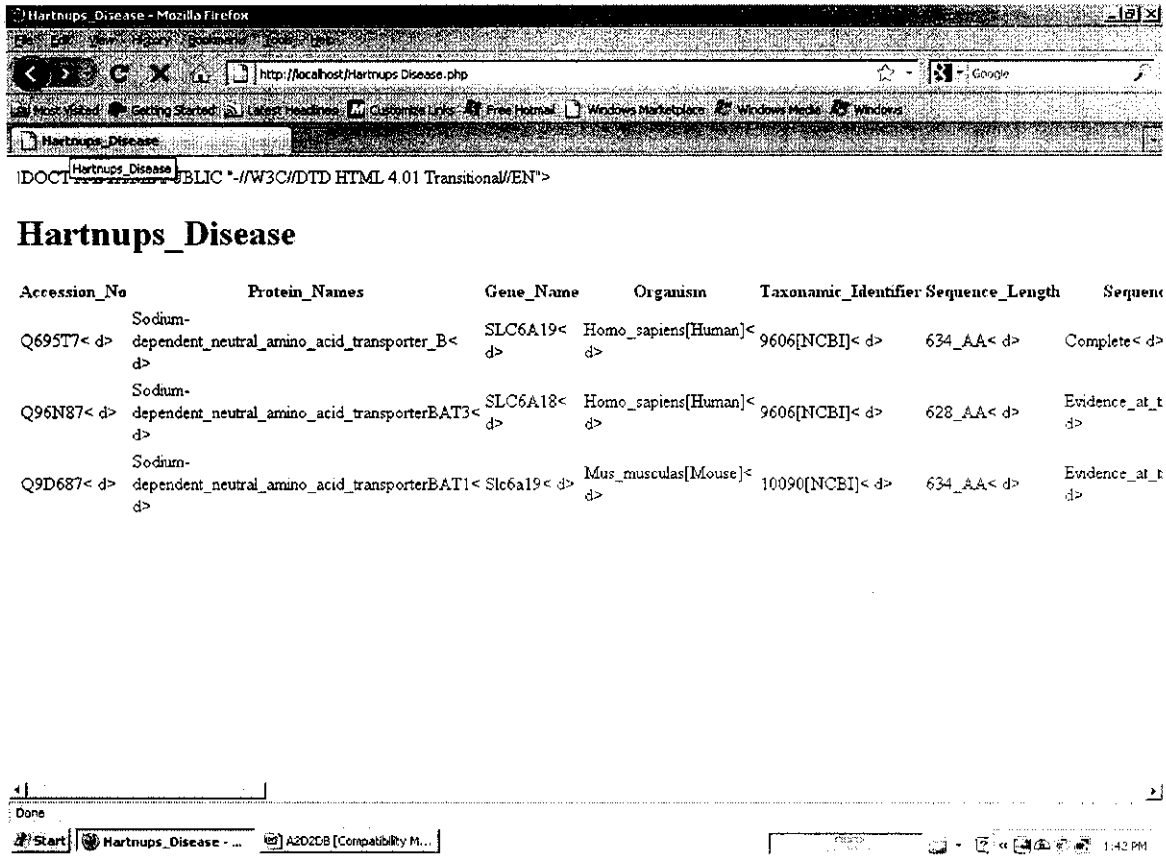
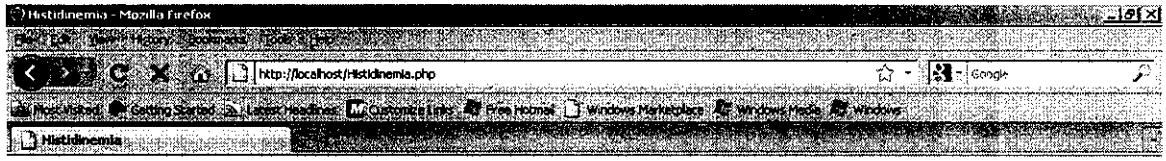


Figure 5.3.6 Information from Hartnup's Disease

5.3.7 Histidinemia



!DOCTYPE HTML PUBLIC "-//W3C//DTD HTML 4.01 Transitional//EN">

Histidinemia

Accession_No	Protein_Names	Gene_Name	Organism	Taxonomic_Identifier	Sequence_Length	Sequence_Status	Pr
P42357< d>	Histidine_ammonia-lyase< d>	HAL< d>	Homo_sapiens[HUMAN]< d>	9606[NCBI]< d>	657_AA< d>	Evidence_at_protein_level< d>	Belongs_to_ d>
P35492< d>	Histidine_ammonia-lyase< d>	Hal< d>	Mus_musculas[Mouse]< d>	10090[NCBI]< d>	657_AA< d>	Evidence_at_protein_level< d>	Belongs_to_
Q2PH55< d>	Histidase< d>	HAL< d>	Homo_sapiens[Human]< d>	9606[NCBI]< d>	46_AA< d>	Evidence_at_transcript_level< d>	Belongs_to_
Q2PH56< d>	Histidase< d>	HAL< d>	Homo_sapiens[Human]< d>	9606[NCBI]< d>	49_AA< d>	Evidence_at_transcript_level< d>	Belongs_to_
Q2PH58< d>	Histidase< d>	HAL< d>	Homo_sapiens[Human]< d>	9606[NCBI]< d>	41_AA< d>	Evidence_at_transcript_level< d>	Belongs_to_
Q2PH57< d>	Histidase< d>	HAL< d>	Homo_sapiens[Human]< d>	9606[NCBI]< d>	46_AA< d>	Evidence_at_transcript_level< d>	Belongs_to_
Q2PH60< d>	Histidase< d>	HAL< d>	Homo_sapiens[Human]< d>	9606[NCBI]< d>	46_AA< d>	Evidence_at_transcript_level< d>	Belongs_to_
Q2PH59< d>	Histidase< d>	HAL< d>	Homo_sapiens[Human]< d>	9606[NCBI]< d>	46_AA< d>	Evidence_at_transcript_level< d>	Belongs_to_

Figure 5.3.7 Information from Histidinemia

5.3.8 Maple syrup urine

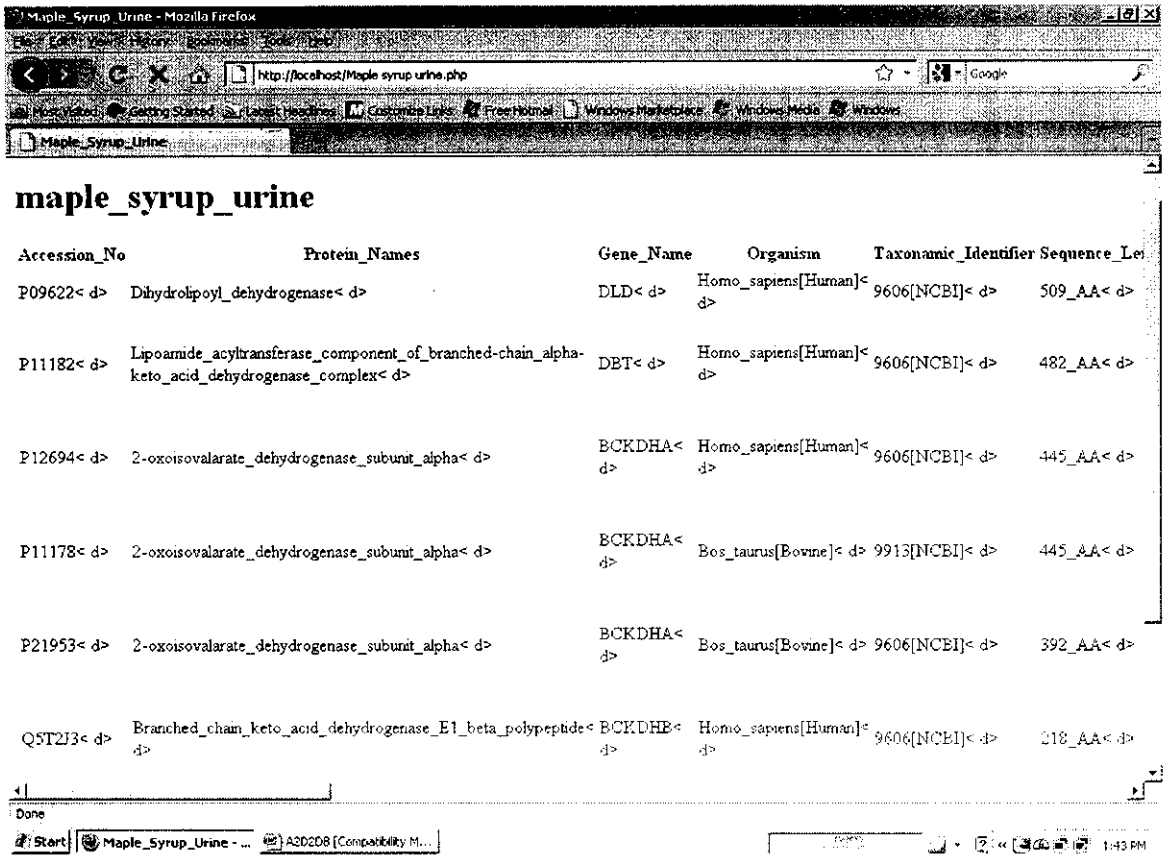
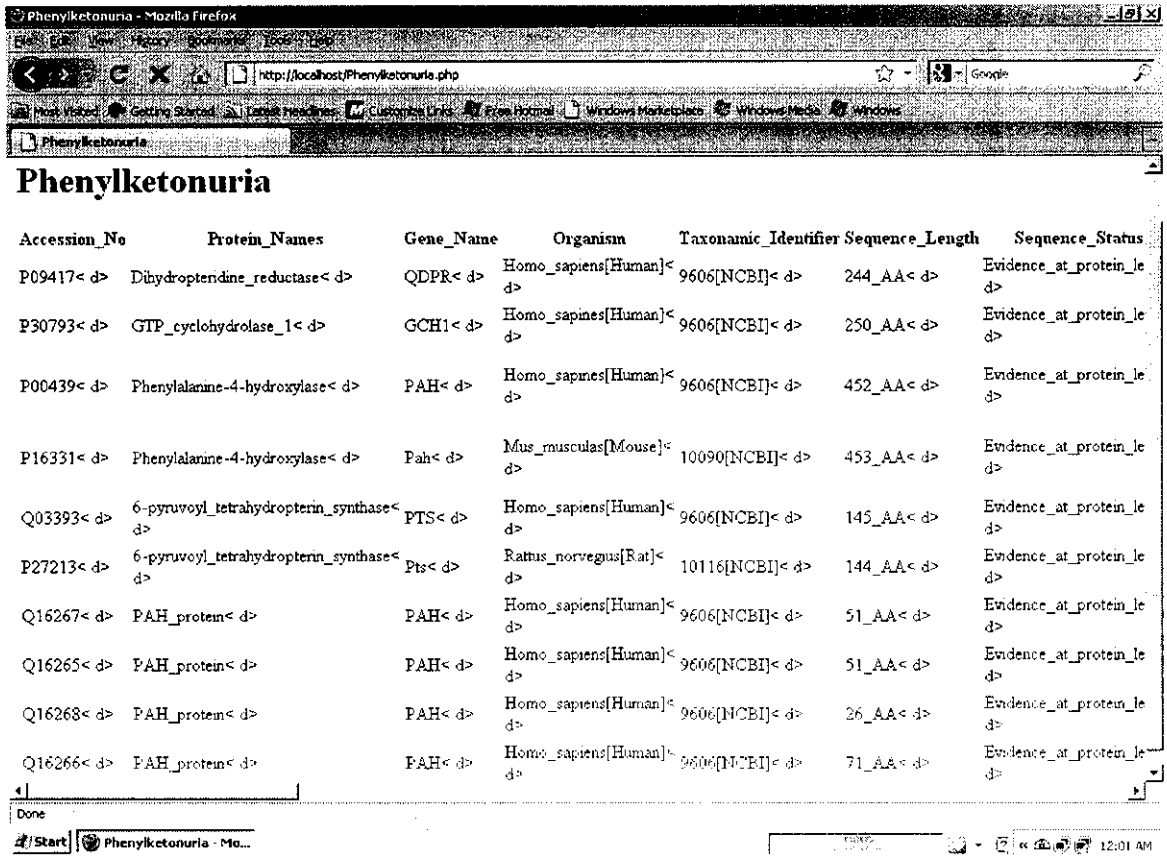


Figure 5.3.8 Information from Maple syrup urine

5.3.9 Phenylketonuria

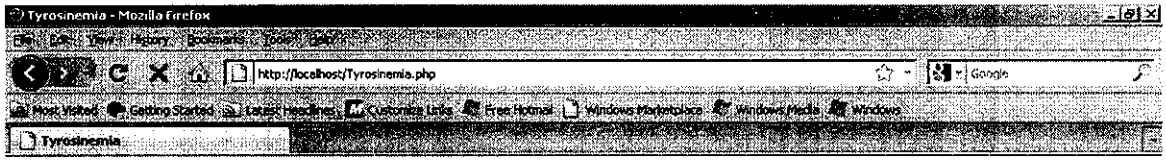


Phenylketonuria

Accession_No	Protein_Names	Gene_Name	Organism	Taxonamic_Identifier	Sequence_Length	Sequence_Status
P09417< d>	Dihydropteridine_reductase< d>	QDPR< d>	Homo_sapiens[Human]< d>	9606[NCBI]< d>	244_AA< d>	Evidence_at_protein_le d>
P30793< d>	GTP_cyclohydrolase_1< d>	GCH1< d>	Homo_sapiens[Human]< d>	9606[NCBI]< d>	250_AA< d>	Evidence_at_protein_le d>
P00439< d>	Phenylalanine-4-hydroxylase< d>	PAH< d>	Homo_sapiens[Human]< d>	9606[NCBI]< d>	452_AA< d>	Evidence_at_protein_le d>
P16331< d>	Phenylalanine-4-hydroxylase< d>	Pah< d>	Mus_musculas[Mouse]< d>	10090[NCBI]< d>	453_AA< d>	Evidence_at_protein_le d>
Q03393< d>	6-pyruvoyl_tetrahydropterin_synthase< d>	PTS< d>	Homo_sapiens[Human]< d>	9606[NCBI]< d>	145_AA< d>	Evidence_at_protein_le d>
P27213< d>	6-pyruvoyl_tetrahydropterin_synthase< d>	Pts< d>	Rattus_norvegus[Rat]< d>	10116[NCBI]< d>	144_AA< d>	Evidence_at_protein_le d>
Q16267< d>	PAH_protein< d>	PAH< d>	Homo_sapiens[Human]< d>	9606[NCBI]< d>	51_AA< d>	Evidence_at_protein_le d>
Q16265< d>	PAH_protein< d>	PAH< d>	Homo_sapiens[Human]< d>	9606[NCBI]< d>	51_AA< d>	Evidence_at_protein_le d>
Q16268< d>	PAH_protein< d>	PAH< d>	Homo_sapiens[Human]< d>	9606[NCBI]< d>	26_AA< d>	Evidence_at_protein_le d>
Q16266< d>	PAH_protein< d>	PAH< d>	Homo_sapiens[Human]< d>	9606[NCBI]< d>	71_AA< d>	Evidence_at_protein_le d>

Figure 5.3.9 Information from Phenylketonuria

5.3.10 Tyrosinemia



!DOCTYPE HTML PUBLIC "-//W3C//DTD HTML 4.01 Transitional//EN">

Tyrosinemia

Accession_No	Protein_Names	Gene_Name	Organism	Taxonomic_Identifier	Sequence_Length	Sequence_Status
P17735< d>	Tyrosine_aminotransferase< d>	TAT< d>	Homo_sapiens[Human]< d>	9606[NCBI]< d>	454_AA< d>	Evidence_at_protein_le d>
P16930< d>	Fumaryl_acetoacetase< d>	FAH< d>	Homo_sapiens[Human]< d>	9606[NCBI]< d>	419_AA< d>	Evidence_at_protein_le d>
P35505< d>	Fumaryl_acetoacetase< d>	Fah< d>	Mus_musculas[Mouse]< d>	9606[NCBI]< d>	393_AA< d>	Evidence_at_protein_le d>
P32754< d>	4-hydroxyphenyl_pyruvate_dioxgenase< d>	HPD< d>	Homo_sapiens[Human]< d>	9606[NCBI]< d>	393_AA< d>	Evidence_at_protein_le d>
P49429< d>	4-hydroxyphenyl_pyruvate_dioxgenase< d>	Hpd< d>	Mus_musculas[Mouse]< d>	9606[NCBI]< d>	393_AA< d>	Evidence_at_protein_le d>
A2QIN6< d>	Hereditary_tyrosinemia_type-1< d>	An04g04150< d>	Aspergillus_niger< d>	425011[NCBI]< d>	405_AA< d>	predicted< d>
Q9XSW4< d>	Tyrosine_aminotransferase< d>	< d>	Mustela_vision< d>	452646[NCBI]< d>	454_AA< d>	Inferred_by_homology<

Figure 5.3.10 Information from Tyrosinemia

Chapter-VI

Conclusion

6. CONCLUSION

A^2D^2DB (Amino Acid Deficiency Disorder Data Base) is about the information on various protein metabolic disorders. Currently the database has 10 protein disorder lists and the protein information can be updated as and when additional data is made available. A^2D^2DB will aid understanding of collective patterns in various diseases which include the diseases, causes, signs & symptoms, prevalence, pathophysiology, treatment and protein details of the particular disease from PROTEIN database such as the SWISSPROT. A^2D^2DB will also give browser which describes the useful data's about the protein disorders. Thus, this online web based database will help researchers and students working with protein metabolic disorders.

Chapter-VII

References

7. REFERENCES

1. Ben. L. N, V. G. Zannoni, L. Laster and J. E. Seegmiller (1958), The nature of the defect in tyrosine metabolism in alcaptonuria, Journal of Biological Chemistry, 230 (1): 251–60.

2. Centerwall, S. A and W. R. Centerwall (2000), The discovery of phenylketonuria: the story of a young couple, two affected children, and a scientist. Pediatrics, 105: 89–103.

3. DiLella. A. G, S. C. M. Kwok, F. D. Ledley, J. Marvit and S. L .C. Woo (1986), Molecular structure and polymorphic map of the human phenylalanine hydroxylase gene, J. Biochem, 25: 743–749.

4. Garrod. A. E (1908), The Croonian lectures on inborn errors of metabolism: lecture II: alkaptonuria, Lancet, 2: 73–79.

5. Greene. M. L, P. S. Lietman, L. E. Rosenberg and J. E. Seegmiller (1973), Familial hyperglycinuria: New defect in renal tubular transport of glycine and imino acids, The American journal of medicine, 54 (2): 265–271.

6. Guldberg. P, K. F. Henriksen, I. Sipila, F. Guttler and D. A. Chapelle (1995), Phenylketonuria in a low incidence population: molecular characterization of mutations in Finland, J. Med. Genet, 32: 976–978.

7. Haas. V, E. C. C Weber and J. B. Klerk (1998), The success of dietary protein restriction in alkaptonuria patients is age-dependent, Journal of Inherited Metabolic Disease, 21(8): 791–8.

8. Hong. E. S, H. Zeeb and M. H. Repacholi (2006), Albinism in Africa as a public health issue, Research article, BMC public health.

9. Incerti. B, K. Cortese, A. Pizzigoni and E. M. Surface (2000), Oa1 Knock-out: new insights on the pathogenesis of ocular albinism type 1, Human Molecular Genetics, 9(19): 2781-2788.

10. Kaser. H, P. Ottier and I. Antener (1962), Glucoglycinuria, a new familial syndrome, The Journal of paediatrics, 61: 386–394.

11. Kobak. A. C, G. Oder, S. Kobak, M. Argin and V. Inal (2005), Ochronotic arthropathy: disappearance of alkaptonuria after liver transplantation for hepatitis B-related cirrhosis, Journal of Clinical Rheumatology, 11(6): 323–5.

12. Leel. T. Y, H. D. Huangl, J. H. Hungl, H. Y. Huangl, Y. S. Yang and T. H. Wang (2006), dbPTM: an information repository of protein post-translational modification, Nucleic Acids Research, 34(8): 520-7

13. Levy H, B. Burton and S. Cederbaum (2007), Recommendations for evaluation of responsiveness to tetrahydrobiopterin (BH (4)) in phenylketonuria and its use in treatment. Mol. Genet. Metab, 92 (4): 287–291.

14. Michals. K and R. Matalon (1985), Phenylalanine metabolites, attention span and hyperactivity, American Journal of Clinical Nutrition, 42(2): 361–365.

15. Oh. H. J, E. S. Park, S. Kang, I. Jo and S. C. Jung (2004), Long-Term Enzymatic and Phenotypic Correction in the Phenylketonuria Mouse Model by Adeno-Associated Virus Vector-Mediated Gene Transfer, Pediatric Research, 56: 278–284.

16. Pietz. J, R. Kreis, A. Rupp, E. Mayatepek, D. Rating, C. Boesch and H. J. Bremer (1999), large neutral amino acids block phenylalanine transport into brain tissue in patients with phenylketonuria, Journal of Clinical Investigation, 103: 1169–1178.

17. Richard. G. A, J. Rogers, M. G. Katze, R. Bumgarner, G. M. Weinstock, E. R. Mardis and K. A. Remington(2007), Evolutionary and Biomedical Insights from the Rhesus Macaque Genome, Science, 316 (5822): 222–234.

18. Saito. T, S. Hayasaka, K. Yabata, K. Omura, K. Mizuno and K. Tada (1981) A typical gyrate atrophy of the choroid and retina and iminoglycinuria, The Tohoku journal of experimental medicine, 135 (3): 331–332.

19. William. D. J, J. Berger and G. Timothy (2006), Andrews' Diseases of the Skin: clinical Dermatology. Saunders Elsevier.

20. Zatkova. A, D. B. Bernabe and H. Polakova (2000), High frequency of alkaptonuria in Slovakia: evidence for the appearance of multiple mutations in HGO involving different mutational hot spots, American Journal of Human Genetics, 67 (5): 1333–9.

Chapter-VIII

Web References

8. WEB REFERENCES

1.) http://www.ncbi.nlm.nih.gov

2.) http://www.umm.edu/article

3.) http://en.wikipedia.org/wiki/metabolic disorders

4.) http://www.medhelp.org

5.) http://www.health-care-guide.org

6.) http://www.medic8.com

7.) http://www.news-medical.net

8.) http://www.medpedia.com

9.) http://www.about.com

10.) http://www.healthinsite.gov.au

Chapter-IX

Annexure

9. ANNEXURE

9.1 Annexure I

List of MYSQL Tables

```
mysql> use a2d2db;

Database changed

mysql> show tables;

+----------------------------+

| Tables_in_a2d2db |

+----------------------------+

| Albinism                   |

| Alkaptonuria               |

| Cystinosis                 |

| Cystinuria                 |

| Glycinuria                 |

| Hartnup`s Disease          |

| Histidinemia               |

| Maple Syrup Urine          |

| Phenylketonuria            |

+----------------------------+

10 rows in set (0.41 sec)
```

```
mysql> desc Albinism;
+---------------+--------------+------+-----+---------+-------+
| Field         | Type         | Null | Key | Default | Extra |
+---------------+--------------+------+-----+---------+-------+
| Accession_No  | varchar(100) | NO   | PRI | 0       |       |
| Protein_Name  | varchar(500) | YES  |     | NULL    |       |
| Gene_Name     | varchar(400) | YES  |     | NULL    |       |
| Organism      | varchar(2000)| YES  |     | NULL    |       |
| Taxonamic_Identifier | varchar(2000) | YES  |     | NULL    |       |
| Sequence_Length | varchar(2000) | YES  |     | NULL    |       |
| Sequence_Status | varchar(100) | YES  |     | NULL    |       |
| Protein_Existence | varchar(100) | YES  |     | NULL    |       |
| Sequence_Similarities | varchar(100) | YES  |     | NULL    |       |
| Biological_Process | varchar(100) | YES  |     | NULL    |       |
| Cellular_Component | varchar(100) | YES  |     | NULL    |       |
| Molecular_Function | varchar(100) | YES  |     | NULL    |       |
| PTM           | varchar(100) | YES  |     | NULL    |       |
| Functions     | varchar(100) | YES  |     | NULL    |       |
| KEGG_Id       | varchar(100) | YES  |     | NULL    |       |
+---------------+--------------+------+-----+---------+-------+
15 rows in set (0.03 sec)
```

```
mysql> desc Alkaptonuria;
+----------------+---------------+------+-----+---------+-------+
| Field          | Type          | Null | Key | Default | Extra |
+----------------+---------------+------+-----+---------+-------+
| Accession_No   | varchar(100)  | NO   | PRI | 0       |       |
| Protein_Name   | varchar(500)  | YES  |     | NULL    |       |
| Gene_Name      | varchar(400)  | YES  |     | NULL    |       |
| Organism       | varchar(2000) | YES  |     | NULL    |       |
| Taxonamic_Identifier | varchar(2000) | YES  |     | NULL    |       |
| Sequence_Length | varchar(2000) | YES  |     | NULL    |       |
| Sequence_Status | varchar(100)  | YES  |     | NULL    |       |
| Protein_Existence | varchar(100)  | YES  |     | NULL    |       |
| Sequence_Similarities | varchar(100)  | YES  |     | NULL    |       |
| Biological_Process | varchar(100)  | YES  |     | NULL    |       |
| Cellular_Component | varchar(100)  | YES  |     | NULL    |       |
| Molecular_Function | varchar(100)  | YES  |     | NULL    |       |
| PTM            | varchar(100)  | YES  |     | NULL    |       |
| Functions      | varchar(100)  | YES  |     | NULL    |       |
| KEGG_Id        | varchar(100)  | YES  |     | NULL    |       |
+----------------+---------------+------+-----+---------+-------+
15 rows in set (0.06 sec)
```

```
mysql> desc Cystinosis;
+-----------------+--------------+------+-----+---------+-------+
| Field           | Type         | Null | Key | Default | Extra |
+-----------------+--------------+------+-----+---------+-------+
| Accession_No    | varchar(100) | NO   | PRI | 0       |       |
| Protein_Name    | varchar(500) | YES  |     | NULL    |       |
| Gene_Name       | varchar(400) | YES  |     | NULL    |       |
| Organism        | varchar(2000)| YES  |     | NULL    |       |
| Taxonamic_Identifier | varchar(2000) | YES |  | NULL    |       |
| Sequence_Length | varchar(2000)| YES  |     | NULL    |       |
| Sequence_Status | varchar(100) | YES  |     | NULL    |       |
| Protein_Existence | varchar(100) | YES |    | NULL    |       |
| Sequence_Similarities | varchar(100) | YES |  | NULL    |       |
| Biological_Process | varchar(100) | YES |   | NULL    |       |
| Cellular_Component | varchar(100) | YES |   | NULL    |       |
| Molecular_Function | varchar(100) | YES |   | NULL    |       |
| PTM             | varchar(100) | YES  |     | NULL    |       |
| Functions       | varchar(100) | YES  |     | NULL    |       |
| KEGG_Id         | varchar(100) | YES  |     | NULL    |       |
+-----------------+--------------+------+-----+---------+-------+
15 rows in set (0.11 sec)
```

```
mysql> desc Cystinuria;
+--------------+--------------+------+-----+---------+-------+
| Field        | Type         | Null | Key | Default | Extra |
+--------------+--------------+------+-----+---------+-------+
| Accession_No | varchar(100) | NO   | PRI | 0       |       |
| Protein_Name | varchar(500) | YES  |     | NULL    |       |
| Gene_Name | varchar(400) | YES  |     | NULL    |       |
| Organism | varchar(2000) | YES  |     | NULL    |       |
| Taxonamic_Identifier | varchar(2000) | YES  |     | NULL    |       |
| Sequence_Length | varchar(2000) | YES  |     | NULL    |       |
| Sequence_Status | varchar(100) | YES  |     | NULL    |       |
| Protein_Existence | varchar(100) | YES  |     | NULL    |       |
| Sequence_Similarities | varchar(100) | YES  |     | NULL    |       |
| Biological_Process | varchar(100) | YES  |     | NULL    |       |
| Cellular_Component | varchar(100) | YES  |     | NULL    |       |
| Molecular_Function | varchar(100) | YES  |     | NULL    |       |
| PTM | varchar(100) | YES  |     | NULL    |       |
| Functions | varchar(100) | YES  |     | NULL    |       |
| KEGG_Id | varchar(100) | YES  |     | NULL    |       |
+--------------+--------------+------+-----+---------+-------+
15 rows in set (0.09 sec)
```

```
mysql> desc Glycinuria;
+----------------+---------------+------+-----+---------+-------+
| Field          | Type          | Null | Key | Default | Extra |
+----------------+---------------+------+-----+---------+-------+
| Accession_No   | varchar(100)  | NO   | PRI | 0       |       |
| Protein_Name   | varchar(500)  | YES  |     | NULL    |       |
| Gene_Name      | varchar(400)  | YES  |     | NULL    |       |
| Organism       | varchar(2000) | YES  |     | NULL    |       |
| Taxonamic_Identifier | varchar(2000) | YES  |     | NULL    |       |
| Sequence_Length | varchar(2000) | YES  |     | NULL    |       |
| Sequence_Status | varchar(100)  | YES  |     | NULL    |       |
| Protein_Existence | varchar(100)  | YES  |     | NULL    |       |
| Sequence_Similarities | varchar(100)  | YES  |     | NULL    |       |
| Biological_Process | varchar(100)  | YES  |     | NULL    |       |
| Cellular_Component | varchar(100)  | YES  |     | NULL    |       |
| Molecular_Function | varchar(100)  | YES  |     | NULL    |       |
| PTM            | varchar(100)  | YES  |     | NULL    |       |
| Functions      | varchar(100)  | YES  |     | NULL    |       |
| KEGG_Id        | varchar(100)  | YES  |     | NULL    |       |
+----------------+---------------+------+-----+---------+-------+
15 rows in set (0.03 sec)
```

```
mysql> desc Hartnup's Disease;
+--------------+--------------+------+-----+---------+-------+
| Field        | Type         | Null | Key | Default | Extra |
+--------------+--------------+------+-----+---------+-------+
| Accession_No | varchar(100) | NO   | PRI | 0       |       |
| Protein_Name | varchar(500) | YES  |     | NULL    |       |
| Gene_Name    | varchar(400) | YES  |     | NULL    |       |
| Organism     | varchar(2000)| YES  |     | NULL    |       |
| Taxonamic_Identifier | varchar(2000) | YES |  | NULL |  |
| Sequence_Length | varchar(2000) | YES |  | NULL |  |
| Sequence_Status | varchar(100) | YES |  | NULL |  |
| Protein_Existence | varchar(100) | YES |  | NULL |  |
| Sequence_Similarities | varchar(100) | YES |  | NULL |  |
| Biological_Process | varchar(100) | YES |  | NULL |  |
| Cellular_Component | varchar(100) | YES |  | NULL |  |
| Molecular_Function | varchar(100) | YES |  | NULL |  |
| PTM | varchar(100) | YES |  | NULL |  |
| Functions | varchar(100) | YES |  | NULL |  |
| KEGG_Id | varchar(100) | YES |  | NULL |  |
+--------------+--------------+------+-----+---------+-------+
15 rows in set (0.06 sec)
```

```
mysql> desc Histidinemia;
+--------------+--------------+------+-----+---------+-------+
| Field        | Type         | Null | Key | Default | Extra |
+--------------+--------------+------+-----+---------+-------+
| Accession_No | varchar(100) | NO   | PRI | 0       |       |
| Protein_Name | varchar(500) | YES  |     | NULL    |       |
| Gene_Name    | varchar(400) | YES  |     | NULL    |       |
| Organism     | varchar(2000)| YES  |     | NULL    |       |
| Taxonamic_Identifier | varchar(2000) | YES  |     | NULL    |       |
| Sequence_Length | varchar(2000) | YES  |     | NULL    |       |
| Sequence_Status | varchar(100) | YES  |     | NULL    |       |
| Protein_Existence | varchar(100) | YES  |     | NULL    |       |
| Sequence_Similarities | varchar(100) | YES  |     | NULL    |       |
| Biological_Process | varchar(100) | YES  |     | NULL    |       |
| Cellular_Component | varchar(100) | YES  |     | NULL    |       |
| Molecular_Function | varchar(100) | YES  |     | NULL    |       |
| PTM          | varchar(100) | YES  |     | NULL    |       |
| Functions    | varchar(100) | YES  |     | NULL    |       |
| KEGG_Id      | varchar(100) | YES  |     | NULL    |       |
+--------------+--------------+------+-----+---------+-------+
15 rows in set (0.04 sec)
```

mysql> desc Maple syrup urine;

Field	Type	Null	Key	Default	Extra
Accession_No	varchar(100)	NO	PRI	0	
Protein_Name	varchar(500)	YES		NULL	
Gene_Name	varchar(400)	YES		NULL	
Organism	varchar(2000)	YES		NULL	
Taxonamic_Identifier	varchar(2000)	YES		NULL	
Sequence_Length	varchar(2000)	YES		NULL	
Sequence_Status	varchar(100)	YES		NULL	
Protein_Existence	varchar(100)	YES		NULL	
Sequence_Similarities	varchar(100)	YES		NULL	
Biological_Process	varchar(100)	YES		NULL	
Cellular_Component	varchar(100)	YES		NULL	
Molecular_Function	varchar(100)	YES		NULL	
PTM	varchar(100)	YES		NULL	
Functions	varchar(100)	YES		NULL	
KEGG_Id	varchar(100)	YES		NULL	

15 rows in set (0.11 sec)

```
mysql> desc Phenylketonuria;
+-----------------+--------------+------+-----+---------+-------+
| Field           | Type         | Null | Key | Default | Extra |
+-----------------+--------------+------+-----+---------+-------+
| Accession_No    | varchar(100) | NO   | PRI | 0       |       |
| Protein_Name    | varchar(500) | YES  |     | NULL    |       |
| Gene_Name       | varchar(400) | YES  |     | NULL    |       |
| Organism        | varchar(2000)| YES  |     | NULL    |       |
| Taxonamic_Identifier | varchar(2000) | YES |  | NULL    |       |
| Sequence_Length | varchar(2000)| YES  |     | NULL    |       |
| Sequence_Status | varchar(100) | YES  |     | NULL    |       |
| Protein_Existence | varchar(100) | YES |    | NULL    |       |
| Sequence_Similarities | varchar(100) | YES |  | NULL    |       |
| Biological_Process | varchar(100) | YES |   | NULL    |       |
| Cellular_Component | varchar(100) | YES |   | NULL    |       |
| Molecular_Function | varchar(100) | YES |   | NULL    |       |
| PTM             | varchar(100) | YES  |     | NULL    |       |
| Functions       | varchar(100) | YES  |     | NULL    |       |
| KEGG_Id         | varchar(100) | YES  |     | NULL    |       |
+-----------------+--------------+------+-----+---------+-------+
15 rows in set (0.06 sec)
```

```
mysql> desc Tyrosinemia;
+--------------+--------------+------+-----+---------+-------+
| Field        | Type         | Null | Key | Default | Extra |
+--------------+--------------+------+-----+---------+-------+
| Accession_No | varchar(100) | NO   | PRI | 0       |       |
| Protein_Name | varchar(500) | YES  |     | NULL    |       |
| Gene_Name    | varchar(400) | YES  |     | NULL    |       |
| Organism     | varchar(2000)| YES  |     | NULL    |       |
| Taxonamic_Identifier | varchar(2000) | YES |  | NULL |  |
| Sequence_Length | varchar(2000) | YES |  | NULL |  |
| Sequence_Status | varchar(100) | YES |  | NULL |  |
| Protein_Existence | varchar(100) | YES |  | NULL |  |
| Sequence_Similarities | varchar(100) | YES |  | NULL |  |
| Biological_Process | varchar(100) | YES |  | NULL |  |
| Cellular_Component | varchar(100) | YES |  | NULL |  |
| Molecular_Function | varchar(100) | YES |  | NULL |  |
| PTM | varchar(100) | YES |  | NULL |  |
| Functions | varchar(100) | YES |  | NULL |  |
| KEGG_Id | varchar(100) | YES |  | NULL |  |
+--------------+--------------+------+-----+---------+-------+
15 rows in set (0.03 sec)
```

9.2 Annexure II

List of PHP Scripts

Albinism

```
! DOCTYPE HTML PUBLIC "-//W3C//DTD HTML 4.01 Transitional//EN">
<html>
<head>
<meta http-equiv="Content-Type" content="text/html;
 charset=iso-8859-1"/>
<title>Albinism</title>
</head>
<body>
<h1>Albinism</h1>
<table>
<tr>
 <th>Accession_No</th>
 <th>Protein_Names</th>
 <th>Gene_Name</th>
 <th>Organism</th>
<th>Taxonamic_Identifier</th>
<th>Sequence_Length</th>
 <th>Sequence_Status</th>
 <th>Protein_Existence</th>
 <th>Sequence_similarities</th>
 <th>Biological_Processes</th>
```

```
<th>Cellular_component</th>
<th>Molecular_function</th>
<th>PTM</th>
<th>Functions</th>
<th>KEGG</th>
</tr>
<?php
//Connect to the MySQL server
if(!($connection=@mysql_connect("localhost","root","")))
 die("cannot connect");
 if(!(mysql_select_db("A2d2db",$connection)))
 die("could't select A2d2db database");
 //Run the query on the connection
 if(!($result=@mysql_query("SELECT * FROM Albinism",$connection)))
 die("couldn't run the query");
 //Until there are no rows in the result set, fetch a row into the $row array and...
 while($row=@mysql_fetch_array($result,MYSQL_ASSOC))
 {
 //Start a table row
 print "<tr>\n";
 //... and print out each of the columns
 foreach($row as $data)
 print "\t<td>{$data}<\td>\n";
 //Finish the row
```

```
print "</tr>\n";
}
?>
</table>
</body>
</html>
```

Alkaptonuria

```
! DOCTYPE HTML PUBLIC "-//W3C//DTD HTML 4.01 Transitional//EN">
<html>
<head>
<meta http-equiv="Content-Type" content="text/html;
 charset=iso-8859-1"/>
<title>Alkaptonuria</title>
</head>
<body>
<h1>Alkaptonuria</h1>
<table>
<tr>
 <th>Accession_No</th>
 <th>Protein_Names</th>
 <th>Gene_Name</th>
 <th>Organism</th>
<th>Taxonamic_Identifier</th>
<th>Sequence_Length</th>
```

```
<th>Sequence_Status</th>
<th>Protein_Existence</th>
<th>Sequence_similarities</th>
<th>Biological_Processes</th>
<th>Cellular_component</th>
<th>Molecular_function</th>
<th>PTM</th>
<th>Functions</th>
<th>KEGG</th>
</tr>
<?php
//Connect to the MySQL server
if(!($connection=@mysql_connect("localhost","root","")))
die("cannot connect");
if(!(mysql_select_db("A2d2db",$connection)))
die("could't select A2d2db database");
//Run the query on the connection
if(!($result=@mysql_query("SELECT * FROM Alkaptonuria",$connection)))
die("couldn't run the query");
//Until there are no rows in the result set, fetch a row into the $row array and...
while($row=@mysql_fetch_array($result,MYSQL_ASSOC))
{
//Start a table row
print "<tr>\n";
```

```
//... and print out each of the columns
foreach($row as $data)
print "\t<td>{$data}<\td>\n";
//Finish the row
print "</tr>\n";
}
?>
</table>
</body>
</html>
```

Cystinosis

```
! DOCTYPE HTML PUBLIC "-//W3C//DTD HTML 4.01 Transitional//EN">
<html>
<head>
<meta http-equiv="Content-Type" content="text/html;
 charset=iso-8859-1"/>
<title>Cystinosis</title>
</head>
<body>
<h1>Cystinosis</h1>
<table>
<tr>
 <th>Accession_No</th>
 <th>Protein_Names</th>
```

```
<th>Gene_Name</th>
<th>Organism</th>
<th>Taxonamic_Identifier</th>
<th>Sequence_Length</th>
<th>Sequence_Status</th>
<th>Protein_Existence</th>
<th>Sequence_similarities</th>
<th>Biological_Processes</th>
<th>Cellular_component</th>
<th>Molecular_function</th>
<th>PTM</th>
<th>Functions</th>
<th>KEGG</th>
</tr>
<?php
//Connect to the MySQL server
if(!($connection=@mysql_connect("localhost","root","")))
die("cannot connect");
if(!(mysql_select_db("A2d2db",$connection)))
die("could't select A2d2db database");
//Run the query on the connection
if(!($result=@mysql_query("SELECT * FROM Cystinosis",$connection)))
die("couldn't run the query");
//Until there are no rows in the result set, fetch a row into the $row array and...
```

```
while($row=@mysql_fetch_array($result,MYSQL_ASSOC))
{
//Start a table row
print "<tr>\n";
//... and print out each of the columns
foreach($row as $data)
print "\t<td>{$data}<\td>\n";
//Finish the row
print "</tr>\n";
}
?>
</table>
</body>
</html>
```

Cystinuria

```
! DOCTYPE HTML PUBLIC "-//W3C//DTD HTML 4.01 Transitional//EN">
<html>
<head>
<meta http-equiv="Content-Type" content="text/html;
 charset=iso-8859-1"/>
<title>Cystinuria</title>
</head>
<body>
<h1>Cystinuria</h1>
```

```
<table>
<tr>
 <th>Accession_No</th>
 <th>Protein_Names</th>
 <th>Gene_Name</th>
 <th>Organism</th>
<th>Taxonamic_Identifier</th>
<th>Sequence_Length</th>
 <th>Sequence_Status</th>
 <th>Protein_Existence</th>
 <th>Sequence_similarities</th>
 <th>Biological_Processes</th>
<th>Cellular_component</th>
<th>Molecular_function</th>
<th>PTM</th>
<th>Functions</th>
<th>KEGG</th>
</tr>
<?php
//Connect to the MySQL server
if(!($connection=@mysql_connect("localhost","root","")))
 die("cannot connect");
 if(!(mysql_select_db("A2d2db",$connection)))
 die("could't select A2d2db database");
```

```
//Run the query on the connection
if(!($result=@mysql_query("SELECT * FROM Cystinuria",$connection)))
die("couldn't run the query");
//Until there are no rows in the result set, fetch a row into the $row array and...
while($row=@mysql_fetch_array($result,MYSQL_ASSOC))
{
//Start a table row
print "<tr>\n";
//... and print out each of the columns
foreach($row as $data)
print "\t<td>{$data}<\td>\n";
//Finish the row
print "</tr>\n";
}
?>
</table>
</body>
</html>
```

Glycinuria

```
! DOCTYPE HTML PUBLIC "-//W3C//DTD HTML 4.01 Transitional//EN">
<html>
<head>
<meta http-equiv="Content-Type" content="text/html;
 charset=iso-8859-1"/>
```

<title>Glycinuria</title>

</head>

<body>

<h1>Glycinuria</h1>

<table>

<tr>

<th>Accession_No</th>

<th>Protein_Names</th>

<th>Gene_Name</th>

<th>Organism</th>

<th>Taxonamic_Identifier</th>

<th>Sequence_Length</th>

<th>Sequence_Status</th>

<th>Protein_Existence</th>

<th>Sequence_similarities</th>

<th>Biological_Processes</th>

<th>Cellular_component</th>

<th>Molecular_function</th>

<th>PTM</th>

<th>Functions</th>

<th>KEGG</th>

</tr>

<?php

//Connect to the MySQL server

```
if(!($connection=@mysql_connect("localhost","root","")))
 die("cannot connect");
 if(!(mysql_select_db("A2d2db",$connection)))
 die("could't select A2d2db database");
 //Run the query on the connection
 if(!($result=@mysql_query("SELECT * FROM Glycinuria",$connection)))
 die("couldn't run the query");
 //Until there are no rows in the result set, fetch a row into the $row array and...
 while($row=@mysql_fetch_array($result,MYSQL_ASSOC))
 {
 //Start a table row
 print "<tr>\n";
 //... and print out each of the columns
 foreach($row as $data)
 print "\t<td>{$data}<\td>\n";
 //Finish the row
 print "</tr>\n";
 }
?>
</table>
</body>
</html>
```

Hartnup's Disease

```
! DOCTYPE HTML PUBLIC "-//W3C//DTD HTML 4.01 Transitional//EN">
<html>
<head>
<meta http-equiv="Content-Type" content="text/html;
 charset=iso-8859-1"/>
<title>Hartnup's_Disease</title>
</head>
<body>
<h1>Hartnup's_Disease</h1>
<table>
<tr>
 <th>Accession_No</th>
 <th>Protein_Names</th>
 <th>Gene_Name</th>
 <th>Organism</th>
<th>Taxonamic_Identifier</th>
<th>Sequence_Length</th>
 <th>Sequence_Status</th>
 <th>Protein_Existence</th>
 <th>Sequence_similarities</th>
 <th>Biological_Processes</th>
<th>Cellular_component</th>
<th>Molecular_function</th>
```

```
<th>PTM</th>
<th>Functions</th>
<th>KEGG</th>
</tr>
<?php
//Connect to the MySQL server
if(!($connection=@mysql_connect("localhost","root","")))
 die("cannot connect");
 if(!(mysql_select_db("A2d2db",$connection)))
 die("could't select A2d2db database");
 //Run the query on the connection
 if(!($result=@mysql_query("SELECT * FROM Hartnup's_Disease",$connection)))
 die("couldn't run the query");
 //Until there are no rows in the result set, fetch a row into the $row array and...
 while($row=@mysql_fetch_array($result,MYSQL_ASSOC))
 {
 //Start a table row
 print "<tr>\n";
 //... and print out each of the columns
 foreach($row as $data)
 print "\t<td>{$data}<\td>\n";
 //Finish the row
 print "</tr>\n";
 }
```

?>

</table>

</body>

</html>

Histidinemia

! DOCTYPE HTML PUBLIC "-//W3C//DTD HTML 4.01 Transitional//EN">

<html>

<head>

<meta http-equiv="Content-Type" content="text/html;

charset=iso-8859-1"/>

<title>Histidinemia</title>

</head>

<body>

<h1>Histidinemia</h1>

<table>

<tr>

<th>Accession_No</th>

<th>Protein_Names</th>

<th>Gene_Name</th>

<th>Organism</th>

<th>Taxonamic_Identifier</th>

<th>Sequence_Length</th>

<th>Sequence_Status</th>

<th>Protein_Existence</th>

```
<th>Sequence_similarities</th>
<th>Biological_Processes</th>
<th>Cellular_component</th>
<th>Molecular_function</th>
<th>PTM</th>
<th>Functions</th>
<th>KEGG</th>
</tr>
<?php
//Connect to the MySQL server
if(!($connection=@mysql_connect("localhost","root","")))
 die("cannot connect");
 if(!(mysql_select_db("A2d2db",$connection)))
 die("could't select A2d2db database");
 //Run the query on the connection
 if(!($result=@mysql_query("SELECT * FROM Histidinemia",$connection)))
 die("couldn't run the query");
 //Until there are no rows in the result set, fetch a row into the $row array and...
 while($row=@mysql_fetch_array($result,MYSQL_ASSOC))
 {
 //Start a table row
 print "<tr>\n";
 //... and print out each of the columns
 foreach($row as $data)
```

```
print "\t<td>{$data}<\td>\n";
//Finish the row
print "</tr>\n";
}
?>
</table>
</body>
</html>
```

Maple syrup urine

```
! DOCTYPE HTML PUBLIC "-//W3C//DTD HTML 4.01 Transitional//EN">
<html>
<head>
<meta http-equiv="Content-Type" content="text/html;
 charset=iso-8859-1"/>
<title>Maple_Syrup_Urine</title>
</head>
<body>
<h1>Maple_Syrup_Urine</h1>
<table>
<tr>
 <th>Accession_No</th>
 <th>Protein_Names</th>
 <th>Gene_Name</th>
 <th>Organism</th>
```

```
<th>Taxonamic_Identifier</th>
<th>Sequence_Length</th>
 <th>Sequence_Status</th>
 <th>Protein_Existence</th>
 <th>Sequence_similarities</th>
 <th>Biological_Processes</th>
<th>Cellular_component</th>
<th>Molecular_function</th>
<th>PTM</th>
<th>Functions</th>
<th>KEGG</th>
</tr>
<?php
//Connect to the MySQL server
if(!($connection=@mysql_connect("localhost","root","")))
 die("cannot connect");
 if(!(mysql_select_db("A2d2db",$connection)))
 die("could't select A2d2db database");
 //Run the query on the connection
 if(!($result=@mysql_query("SELECT * FROM Maple_Syrup_Urine",$connection)))
 die("couldn't run the query");
 //Until there are no rows in the result set, fetch a row into the $row array and...
 while($row=@mysql_fetch_array($result,MYSQL_ASSOC))
 {
```

```
//Start a table row
print "<tr>\n";
//... and print out each of the columns
foreach($row as $data)
print "\t<td>{$data}<\td>\n";
//Finish the row
print "</tr>\n";
}
?>
</table>
</body>
</html>
```

Phenylketonuria

```
! DOCTYPE HTML PUBLIC "-//W3C//DTD HTML 4.01 Transitional//EN">
<html>
<head>
<meta http-equiv="Content-Type" content="text/html;
 charset=iso-8859-1"/>
<title>Phenylketonuria</title>
</head>
<body>
<h1>Phenylketonuria</h1>
<table>
<tr>
```

```
<th>Accession_No</th>
<th>Protein_Names</th>
<th>Gene_Name</th>
<th>Organism</th>
<th>Taxonamic_Identifier</th>
<th>Sequence_Length</th>
<th>Sequence_Status</th>
<th>Protein_Existence</th>
<th>Sequence_similarities</th>
<th>Biological_Processes</th>
<th>Cellular_component</th>
<th>Molecular_function</th>
<th>PTM</th>
<th>Functions</th>
<th>KEGG</th>
</tr>
<?php
//Connect to the MySQL server
if(!($connection=@mysql_connect("localhost","root","")))
 die("cannot connect");
 if(!(mysql_select_db("A2d2db",$connection)))
 die("could't select A2d2db database");
 //Run the query on the connection
 if(!($result=@mysql_query("SELECT * FROM Phenylketonuria",$connection)))
```

```
die("couldn't run the query");
//Until there are no rows in the result set, fetch a row into the $row array and...
while($row=@mysql_fetch_array($result,MYSQL_ASSOC))
{
//Start a table row
print "<tr>\n";
//... and print out each of the columns
foreach($row as $data)
print "\t<td>{$data}<\td>\n";
//Finish the row
print "</tr>\n";
}
?>
</table>
</body>
</html>
```

Tyrosinemia

```
! DOCTYPE HTML PUBLIC "-//W3C//DTD HTML 4.01 Transitional//EN">
<html>
<head>
<meta http-equiv="Content-Type" content="text/html;
 charset=iso-8859-1"/>
<title>Tyrosinemia</title>
</head>
```

```
<body>
<h1>Tyrosinemia</h1>
<table>
<tr>
 <th>Accession_No</th>
 <th>Protein_Names</th>
 <th>Gene_Name</th>
 <th>Organism</th>
<th>Taxonamic_Identifier</th>
<th>Sequence_Length</th>
 <th>Sequence_Status</th>
 <th>Protein_Existence</th>
 <th>Sequence_similarities</th>
 <th>Biological_Processes</th>
<th>Cellular_component</th>
<th>Molecular_function</th>
<th>PTM</th>
<th>Functions</th>
<th>KEGG</th>
</tr>
<?php
//Connect to the MySQL server
if(!($connection=@mysql_connect("localhost","root","")))
 die("cannot connect");
```

```
if(!(mysql_select_db("A2d2db",$connection)))
die("could't select A2d2db database");
//Run the query on the connection
if(!($result=@mysql_query("SELECT * FROM Tyrosinemia",$connection)))
die("couldn't run the query");
//Until there are no rows in the result set, fetch a row into the $row array and...
while($row=@mysql_fetch_array($result,MYSQL_ASSOC))
{
//Start a table row
print "<tr>\n";
//... and print out each of the columns
foreach($row as $data)
print "\t<td>{$data}<\td>\n";
//Finish the row
print "</tr>\n";
}
?>
</table>
</body>
</html>
```