WEB REPOSITORY FOR MITOCHONDRIAL AND NEUROLOGICAL ASSOCIATED HUMAN DISEASE

Enrollment. No. - 081501, 081509

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May -2012

Submitted in partial fulfillment of the Degree of Bachelor of Technology

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CERTIFICATE

This is to certify that the thesis entitled "**WEB REPOSITORY FOR MITOCHONDRIAL AND NEUROLOGICAL ASSOCIATED HUMAN DISEASE**" submitted by **Gautam Mehta (081501) and Ankit Gupta(081509)** in partial fulfillment of the requirements for the award of the degree of **Bachelor of Technology in Bioinformatics** of Jaypee University of Information Technology, Waknaghat has been carried out under my supervision. This work has not been submitted partially or wholly to any other University or Institute for the award of this or any other degree or diploma.

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ACKNOWLEDGEMENT

This dissertation would not have been possible without the guidance and the help of several individuals who in one way or another contributed and extended their valuable assistance in the preparation and completion of this study.

First and foremost, my utmost gratitude to Dr. Tiratha Raj Singh, Senior Lecturer of the Department of Bioinformatics and Biotechnology (JUIT), for his unfailing support as my project adviser, his patience and steadfast encouragement to complete this study. He has been an inspiration as we hurdled through all the obstacles in the completion this research work.

Dr. R. S. Chauhan, Head of the Department of Biotechnology and Bioinformatics (JUIT), who had kind concern and consideration regarding our academic requirements. We thank Mrs. Somlata Sharma (Bioinformatics Laboratory In-charge) for providing her full cooperation with keen interest.

Apart from these, countless events, countless people and several incidents have made a contribution to this project that is indescribable. We again express our gratitude to them. We are indebted to all those who provided reviews and suggestions for improving the results and topics covered in our project, and extend apologies to any one whom we have failed to recognize in this effort of ours. All copyrights and trademarks that are cited in this document remain the property of their respective owners.

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SUMMARY

The plan of the project is to compile a comprehensive web repository for mitochondria associated or involved human disease. Neurological disorders associated with human have also been incorporated as a separate module. We aim to collect and organize data related to various biological, and other relevant information as a single resource. It will be One-Stop-Shop for researchers and academicians working in the area of mitochondrial associate disease and neurological disorders.

We have also implemented a database in the background specifically for the various kinds of biomarker information search and retrieval. We provide a user friendly web interface to the user to search for general as well as specific information related to disease or marker associated with mitochondria and neurological disorders. Information related to genes, and proteins associated with above mentioned diseases and disorders have been collected, curated, and compiled to make this repository comprehensive and useful.

The database will provide users information as per their need and will help them to extract information regarding marker associated with disease/disorder of their choice. We will also collect the basic information to give the geographical distribution and population statistical ratio of the diseases included in this repository whereas, marker information associated with mitochondrial and neurological disorders will contain gene and protein information along with their hyperlinks to their original resources so user can fetch more information if required. For genetic associated information of the diseases, we have provided hyperlinked OMIM IDs for all the markers to the OMIM database.

Gautam Mehta Ankit

Signature of Students

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CHAPTER – 1
INTRODUCTION

1.1 MITOCHONDRIA:

Mitochondria are like little "factories" in each of the cells of the body that are responsible for making 95% of the body's source of energy. The cells in the body, and especially in organs such as the brain, heart, muscle, kidneys and liver, cannot function normally unless they are receiving a constant supply of energy. The energy is produced in the form of ATP (adenosine tri phosphate) that is used by the body to drive the various reactions essential for body functioning, growth and development (1). A number of biochemical reactions that occur in an ordered sequence within the mitochondria are responsible for this process of ATP production. These reactions are under the control of special proteins called enzymes. The genes found within the mitochondria codes for the production of some of these important enzymes (1, 2).

1.2MITOCONDRIAL DISEASE:

The Mitochondria is the part of the cell responsible for energy production. If the mitochondria are defective, human body cannot function as it should. The brain becomes impaired, muscles start to twitch spastically and weaken, the heart does not pump correctly, vision becomes impaired and the list can go on. For many children and adults with mitochondrial disease, this is exactly what they experience (3).

This energy production is carried out on a complex folded inner membrane of the mitochondria (Fig.1). Every muscle cell is filled with mitochondria, combining sugars or fats with oxygen to yield water and ATP. Without this ATP, human would die, having no "power" left. Mitochondrial cytopathies have a diverse range of symptoms, and span many (all) organ systems (table 1)(4).

Table 1. Problems Associated with Mitochondrial Cytopathies

Organ System	Possible Problems
Brain	Developmental delays, mental retardation, dementia, seizures, neuro-psychiatric disturbances, atypical cerebral palsy, migraines, strokes
Nerves	Weakness (which may be intermittent), neuropathic pain, absent reflexes, gastrointestinal problem (gastroesophogeal reflux, delayed gastric emptying, constipation, pseudo-obstruction), fainting, absent or excessive sweating resulting in temperature regulation problems
Muscles	Weakness, hypotonia, cramping, muscle pain
Kidneys	Proximal renal tubular wasting resulting in loss of protein, magnesium, phosphorous, calcium and other electrolytes
Hear	Cardiac conduction defects (heart blocks), cardiomyopathy
Liver	Hypoglycemia (low blood sugar), liver failure
Eyes	Visual loss and blindness
Ears	Hearing loss and deafness
Pancreas	Diabetes and exocrine pancreatic failure (inability to make digestive enzymes)
Systemic	Failure to gain weight, short stature, fatigue, respiratory problems including intermittent air hunger

This table shows a basic idea of how this can happen. Here's the simplest way to explain what happens. The food we eat gets broken down and assigned in various fashion. The fats and sugars go through processing, and there's quite a bit involved in this. If you get into this stuff more, you'll hear all about the respiratory chain and ATP, which is the end result, or energy (5). The mitochondria in a cell have to go through five "complexes" to create energy. An error in any of those complexes is bad, but obviously there can be varying degrees of how big the error is, and where it occurs in the energy making process. Mitochondria are responsible for producing 95% of the energy that's needed for our cells to function. In fact,

they provide such an important source of energy that a typical human cell contains hundreds of them (6).

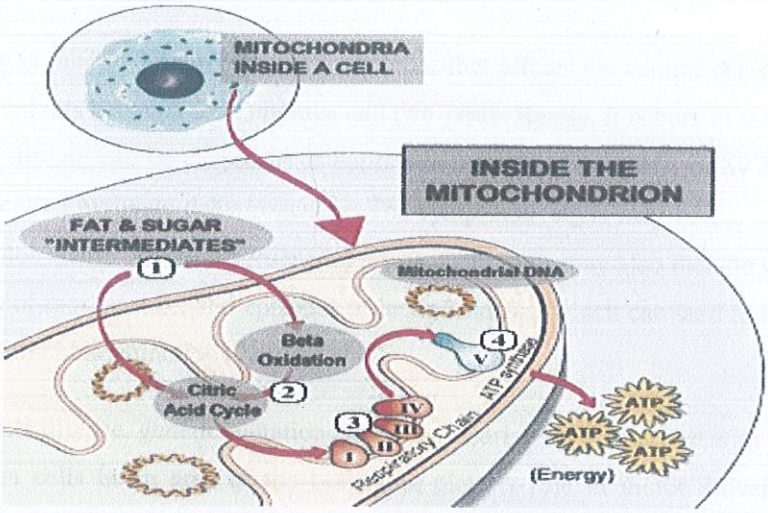


Fig 1: Process of disease in mitochondria

1.3 TYPES OF MITOCHONDRIAL DISEASE:

BARTH SYNDROME:

Barth syndrome (BTHS) is a rare, genetic disorder of lipid metabolism that primarily affects males. It is caused by a mutation in the tafazzin gene (TAZ, also called G4.5) which leads to decreased production of an enzyme required to produce cardiolipin. Cardiolipin is an essential lipid that is important in energy metabolism. Its main characteristics often include combinations in varying degrees of cardiomyopathy (a disorder of the heart muscle), neutropenia (a reduction in the number of white blood cells which lead to an increased risk for bacterial infections), muscle weakness, undeveloped skeletal muscles, delayed growth, lack of stamina, varying degrees of physical disability, BTHS is an X-linked genetic condition passed from mother to son through the X chromosome. A mother who is a carrier of BTHS shows no signs or symptoms of the disorder herself. On average, 50 percent of children born to a carrier mother will inherit the defective gene, but only boys will develop symptoms. All daughters born to an affected male will be carriers.

LEIGH SYNDROME:

Leigh's disease is inherited neuro metabolic disorder that affects the central nervous system. This begins in infants between three months and two years. Rarely, it occurs in teenagers and adults. Leigh's disease can be caused by mutations in mitochondrial DNA or by deficiencies of an enzyme called pyruvate dehydrogenase .The symptoms signs may be the loss of head control and motor skills. As the disorder progresses, symptoms may also include generalized weakness, lack of muscle tone, and episodes of lactic acidosis, which can lead to impairment of respiratory and kidney function (7).

In Leigh's disease, genetic mutations in mitochondrial DNA interfere with the energy sources that run cells in an area of the brain that plays a role in motor movements. The primary function of mitochondria is to convert the energy in glucose and fatty acids into a substance called adenosine triphosphate (ATP). The energy in ATP drives virtually all of a cell's metabolic functions.

Genetic mutations in mitochondrial DNA, therefore, result in a chronic lack of energy in these cells, which in turn affects the central nervous system and causes progressive degeneration of motor functions. There is also a form of Leigh's disease (called X-linked Leigh's disease) which is the result of mutations in a gene. The gene is only found on the X chromosome (8).

PEARSON SYNDROME:

Pearson et al described a previously unrecognized, often fatal disorder of infants with transfusion-dependent sideroblastic anemia and exocrine pancreatic insufficiency. The large deletions of the mitochondrial genome that cause the disorder were discovered a decade later. Pearson syndrome is currently recognized as a rare, multi systemic, mitochondrial cytopathy. Its features are refractory sideroblastic anemia, defective oxidative phosphorylation and variable hepatic, renal, and endocrine failure. Death often occurs in infancy or early childhood due to infection or metabolic crisis.

ALZHEIMERS DISEASE:

Alzheimer's disease is an irreversible, progressive brain disease that slowly destroys memory and thinking skills, and eventually even the ability to carry out the simplest tasks. In most

people with Alzheimer's, symptoms first appear after age 60. Alzheimer's disease is the most common cause of dementia among older people. Dementia is the loss of cognitive functioning such as thinking, remembering, and reasoning, and behavioral abilities, to such an extent that it interferes with a person's daily life and activities.

Alzheimer's disease is named after Dr. Alois Alzheimer. In 1906, Dr. Alzheimer noticed changes in the brain tissue of a woman who had died of an unusual mental illness. Her symptoms included memory loss, language problems, and unpredictable behavior (9-11). After she died, he examined her brain and found many abnormal clumps (now called amyloid plaques) and tangled bundles of fibers (now called neurofibrillary tangles). Plaques and tangles in the brain are two of the main features of Alzheimer's disease. The third is the loss of connections between nerve cells (neurons) in the brain (12-13).

PARKINSON DISEASE:

Parkinson's disease (PD) belongs to a group of conditions called motor system disorders, which are the result of the loss of dopamine-producing brain cells. The four primary symptoms of PD are trembling in hands, arms, legs, and face; rigidity, or stiffness of the limbs and trunk; bradykinesia (slowness of movement); and impaired balance and coordination. When these symptoms become more pronounced, patients may have difficulty walking, talking etc. Other symptoms may include depression and other emotional changes; difficulty in swallowing, chewing, and speaking; urinary problems, skin problems; and sleep disruptions (14). There are currently no blood or laboratory tests that have been proven to help in diagnosing sporadic PD. The disease can be difficult to diagnose accurately. Doctors may sometimes request brain scans or laboratory tests in order to rule out other diseases.

CARDIOMYOPATHY

Cardiomyopathy, or heart muscle disease, is a type of progressive heart disease in which the heart is abnormally enlarged, thickened or rigid. As a result, the heart muscle's ability to pump blood is weakened, often causing heart failure and the backup of blood into the lungs or rest of the body (15). The disease can also cause abnormal heart rhythms.

Usually, Cardiomyopathy begins in the heart's lower chambers (the ventricles), but in severe cases can affect the upper chambers, or atria. The weakening of the heart also can

cause other complications, such as heart valve problems. The main types of Cardiomyopathy are:

- Dilated Cardiomyopathy
- Hypertrophic Cardiomyopathy
- Restrictive Cardiomyopathy
- Arrhythmogenic right ventricular dysplasia

MITOCHONDRIAL ENCEPHALOPATHY (MELAS)

MELAS syndrome is caused by mutations in the genetic material (DNA) in the mitochondria. While most of our DNA is in the chromosomes in the cell nucleus, some of our DNA is in another important structure called mitochondria.

Each mitochondrion has a chromosome made of DNA that is quite different from the better known chromosomes in the nucleus. The mitochondrial chromosome is much smaller; it is round (whereas the chromosomes in the nucleus are normally shaped like rods); there are many copies of the mitochondrial chromosome in every cell; and no matter whether we are male or female, we inherit our entire mitochondrial chromosome from our mother. Much of the DNA in our mitochondria is used to manufacture proteins involved in the key function of mitochondria - to produce energy and power the cells in our body.

FRIEDREICH'S ATAXIA

Friedreich's ataxia is an inherited disease that damages your nervous system. The damage affects your spinal cord and the nerves that control muscle movement in your arms and legs. Symptoms usually begin between the ages of 5 and 15 (16-18). The main symptom is ataxia, which means trouble coordinating movements. Specific symptoms include

- Difficulty walking
- Muscle weakness
- Speech problems
- Involuntary eye movements
- Scoliosis

People with Friedreich's ataxia usually need a wheelchair 15 to 20 years after symptoms first appear. In severe cases, people become incapacitated. There is no cure. You can treat symptoms with medicines, braces, surgery and physical therapy (19-21).

WILSON'S DISEASE

Wilson disease is a rare autosomal recessive inherited disorder of copper metabolism. The condition is characterized by excessive deposition of copper in the liver, brain, and other tissues. The major physiologic aberration is excessive absorption of copper from the small intestine and decreased excretion of copper by the liver.

The genetic defect, localized to arm 13q, has been shown to affect the copper-transporting adenosine triphosphatase (ATPase) gene (ATP7B) in the liver. Patients with Wilson disease more often initially present with hepatic manifestations when identified in the first decade of life as compared with more neuropsychiatric illness later, and the latter most commonly occurs during the third decade.

Although it is extremely rare in clinical practice, Wilson disease is important because it is often fatal if not recognized and treated when symptomatic. Often, the diagnosis is not made until adulthood, despite manifestations of the disease beginning to develop in childhood.

KEARNS-SAYRE SYNDROME

Kearns-Sayre syndrome (KSS) is a rare neuromuscular disorder with onset usually before the age of 20 uears. It is the result of abnormalities in the DNA of mitochondria - small rod-like structures found in every cell of the body that produce the energy that drives cellular functions.

The mitochondrial diseases correlate with specific DNA mutations that cause problems with many of the organs and tissues in the body. KSS is characterized by progressive limitation of eye movements until there is complete immobility, accompanied by eyelid droop. It is also associated with abnormal accumulation of pigmented material on the membrane lining the eyes. Additional symptoms may include mild skeletal muscle weakness, heart block (a cardiac conduction defect), short stature, hearing loss, an inability to coordinate voluntary movements (ataxia), impaired cognitive function, and diabetes. Several endocrine disorders can be associated with KSS.

ALPERS-HUTTENLOCHER SYNDROME (AHS)

Alpers-Huttenlocher syndrome is one of the most severe of a group of conditions called the POLG-related disorders. The conditions in this group feature a range of similar signs and symptoms involving muscle-, nerve-, and brain-related functions. Alpers-Huttenlocher syndrome typically becomes apparent in children between ages 2 and 4. People with this condition usually have three characteristic features: recurrent seizures (intractable epilepsy), loss of mental and movement abilities (psychomotor regression), and liver disease.

People with Alpers-Huttenlocher syndrome usually have problems with coordination and balance (ataxia) and disturbances in nerve function (neuropathy). Neuropathy can lead to abnormal or absent reflexes (areflexia). In addition, affected individuals may develop weak muscle tone (hypotonia) that worsens until they lose the ability to control their muscles and movement. People with this condition may have decreased brain function that is demonstrated as sleepiness, inability to concentrate, irritability, or loss of language skills or memory.

MYOCLONIC EPILEPSY AND RAGGED-RED FIBRES(MERRF)

Myoclonic epilepsy with ragged-red fibers (MERRF) is a disorder that affects many parts of the body, particularly muscles and the nervous system. In most cases, the signs and symptoms of this disorder appear during childhood or adolescence. The features of MERRF vary widely among affected individuals, even among members of the same family.

MERRF is characterized by muscle twitches (myoclonus), weakness (myopathy), and progressive stiffness (spasticity). When the muscle cells of affected individuals are stained and viewed under a microscope, these cells usually appear abnormal. These abnormal muscle cells are called ragged-red fibers. Other features of MERRF include recurrent seizures (epilepsy), difficulty coordinating movements (ataxia), People with this condition may also develop hearing loss or optic atrophy, which is the degeneration (atrophy) of the nerve cells that carry visual information from the eyes to the brain.

ALEXANDER DISEASE

Alexander disease is a rare disorder of the nervous system. It is one of a group of disorders, called leukodystrophies that involve the destruction of myelin. Myelin is the fatty covering that insulates nerve fibers and promotes the rapid transmission of nerve impulses. If myelin is not properly maintained, the transmission of nerve impulses could be disrupted. As myelin

deteriorates in leukodystrophies such as Alexander disease, nervous system functions are impaired.

Most cases of Alexander disease begin before age 2 and are described as the infantile form. Signs and symptoms of the infantile form typically include an enlarged brain and head size (megalencephaly), seizures, stiffness in the arms and/or legs (spasticity), intellectual disability, and developmental delay. Less frequently, onset occurs later in childhood (the juvenile form) or in adulthood.

Alexander disease is also characterized by abnormal protein deposits known as Rosenthal fibers. These deposits are found in specialized cells called astroglial cells, which support and nourish other cells in the brain and spinal cord (central nervous system).

1.4 NEUROLOGICAL DISORDER

A neurological disorder is any disorder of the body's nervous system. Structural, biochemical or electrical abnormalities in the brain, spinal cordor other nerves can result in a range of symptoms that include paralysis, muscle weakness, poor coordination, seizures, confusion, pain and altered levels of consciousness. There are many recognized neurological disorders, some relatively common, but many rare. They may be assessed by neurological examination, and studied and treated within the specialities of neurology and clinical neuropsychology (22).

Interventions for neurological disorders include preventative measures, lifestyle changes, physiotherapy or other therapy, Neuro-rehabilitation, pain management, medication, or operations performed by neurosurgeons. The World Health Organization estimated in 2006 that neurological disorders and their direct consequences affect as many as one billion people worldwide, and identified health inequalities and social stigma/discrimination as major factors contributing to the associated disability and suffering.

NEURON

A neuron is an electrically excitable cell that processes and transmits information by electrical and chemical signaling. Chemical signaling occurs via synapses, specialized connections with other cells. Neurons connect to each other to form neural networks. Neurons are the core components of the nervous system, which includes the brain, spinal cord, and peripheral ganglia (23). A number of specialized types of neurons exist: sensory neurons respond to touch, sound, light and numerous other stimuli affecting cells of the sensory organs that then send signals to the spinal cord and brain. Motor neurons receive signals from the brain and spinal cord, cause muscle contractions, and affect glands. Interneurons connect neurons to other neurons within the same region of the brain or spinal cord.

1.5 TYPES OF NEUROLOGICAL DISEASE:

FRONTOTEMPORAL DEMENTIA

Frontotemporal dementia (FTD) describes a clinical syndrome associated with shrinking of the frontal and temporal anterior lobes of the brain. Originally known as Pick's disease, the

name and classification of FTD has been a topic of discussion for over a century. The current designation of the syndrome groups together Pick's disease, primary progressive aphasia, and semantic dementia as FTD. Some doctors propose adding corticobasal degeneration and progressive supranuclear palsy to FTD and calling the group Pick Complex (24).

These designations will continue to be debated. As it is defined today, the symptoms of FTD fall into two clinical patterns that involve either (1) changes in behavior, or (2) problems with language. The first type features behavior that can be either impulsive (disinhibited) or bored and listless (apathetic) and includes inappropriate social behavior; lack of social tact; lack of empathy; distractability; loss of insight into the behaviors of oneself and others; an increased interest in sex; changes in food preferences; agitation or, conversely, blunted emotions; neglect of personal hygiene; repetitive or compulsive behavior, and decreased energy and motivation. The second type primarily features symptoms of language disturbance, including difficulty making or understanding speech, often in conjunction with the behavioral type's symptoms. Spatial skills and memory remain intact. There is a strong genetic component to the disease; FTD often runs in families (25).

AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS) is the most common degenerative disease of the motor neuron system. ALS is also known as motor neurone disease (MND).The cause of ALS is unknown, although 5-10% of cases are familial.

In its classic form, ALS affects motor neurons at 2 or more levels supplying multiple regions of the body. It affects lower motor neurons that reside in the anterior horn of the spinal cord and in the brain stem, corticospinal upper motor neurons that reside in the precentral gyrus; and, frequently, prefrontal motor neurons that are involved in planning or the work of the upper and lower motor neurons.

Loss of lower motor neurons leads to progressive muscle weakness and wasting (atrophy). Loss of corticospinal upper motor neurons may produce stiffness (spasticity), abnormally active reflexes, and pathological reflexes. Loss of prefrontal neurons may result in special forms of cognitive impairment that include, most commonly, executive dysfunction but may also include an altered awareness of social implications of an individual's .The diagnosis of ALS is primarily clinical. Electrodiagnostic testing contributes to the diagnostic accuracy.

ALS is a fatal disease, with median survival of 3-5 years.Aspiration pneumonia and medical complications of immobility contribute to morbidity in patients with ALS. Although ALS is incurable, there are treatments that can prolong meaningful quality of life (see Treatment); therefore, diagnosis is important to patients and families.

PRION DISEASE

Prion diseases belong to group of progressive conditions that affect the nervous system in humans and animals. In people, prion diseases impair brain function, causing memory changes, personality changes, a decline in intellectual function (dementia), and problems with movement that worsen over time. The signs and symptoms of these conditions typically begin in adulthood, and these disorders lead to death within a few months to several years.

Familial prion diseases of humans include classic Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), and fatal insomnia (FI).

LEWY BODY DEMENTIA

Dementia with Lewy bodies (DLB) is one of the most common types of progressive dementia. The central feature of DLB is progressive cognitive decline, combined with three additional defining features: (1) pronounced "fluctuations" in alertness and attention, such as frequent drowsiness, lethargy (2) recurrent visual hallucinations, and (3) Parkinsonian motor symptoms, such as rigidity and the loss of spontaneous movement.

People may also suffer from depression. The symptoms of DLB are caused by the build-up of Lewy bodies – accumulated bits of alpha-synuclein protein -- inside the nuclei of neurons in areas of the brain that control particular aspects of memory and motor control. Researchers don't know exactly why alpha-synuclein accumulates into Lewy bodies or how Lewy bodies cause the symptoms of DLB, but they do know that alpha-synuclein accumulation is also linked to Parkinson's disease and several other disorders, which are referred to as the "synucleinopathies." Lewy bodies are often also found in the brains of people with Parkinson's and Alzheimer's diseases. These findings suggest that either DLB is related to these other causes of dementia or that an individual can have both diseases at the same time.

VASCULAR DEMENTIA

Vascular dementia is the second most common form of dementia after Alzheimer disease (AD). Vascular dementia refers to a subtle, progressive decline in memory and cognitive

functioning. It occurs when the blood supply carrying oxygen and nutrients to the brain is interrupted by a blocked or diseased vascular system. If blood supply is blocked for longer than a few seconds, brain cells can die, causing damage to the cortex of the brain the area associated with learning, memory, and language.

Depending on the person, and the severity of the stroke or strokes, vascular dementia may come on gradually or suddenly. Currently, there is no known cure, but the good news is that making certain lifestyle changes and using practical strategies may help prevent strokes, compensate for cognitive loses, and slow its development.

CORTICOBASAL DEGENERATION

Corticobasal degeneration is a progressive neurological disorder characterized by nerve cell loss and atrophy (shrinkage) of multiple areas of the brain including the cerebral cortex and the basal ganglia. Corticobasal degeneration progresses gradually. Initial symptoms, which typically begin at or around age 60, may first appear on one side of the body (unilateral), but eventually affect both sides as the disease progresses. Symptoms are similar to Parkinson disease, such as poor coordination, akinesia (an absence of movements), rigidity (a resistance to imposed movement), disequilibrium (impaired balance); and limb dystonia (abnormal muscle postures.An individual with corticobasal degeneration eventually becomes unable to walk.

MULTIPLE SYSTEM ATROPHY

Multiple system atrophy (MSA) is a progressive neurodegenerative disorder characterized by symptoms of autonomic nervous system failure such as fainting spells and bladder control problems, combined with motor control symptoms such as tremor, rigidity, and loss of muscle coordination. MSA affects both men and women primarily in their 50s. Although what causes MSA is unknown, the disorder's symptoms reflect the loss of nerve cells in several different areas in the brain and spinal cord that control the autonomic nervous system and coordinate muscle movements.

HUNTINGTON'S DISEASE

Huntington's disease is an incurable, hereditary brain disorder. It is a devastating brain disorder for which there is no currently 'effective' treatment. Nerve cells become damaged, causing various parts of the brain to deteriorate. The disease affects movement, behavior and cognition. The affected individuals have abilities to walk, think, reason and talk are gradually

eroded to such a point that they eventually become entirely reliant on other people for their care. Huntington's disease has a major emotional, mental, social and economic impact on the lives of patients, as well as their families.It used to be called Huntington's Chorea, because the involuntary movements made by patients with the disease can appear to be like jerky dancing - "chorea".

SPINAL MUSCULAR ATROPHY(SMA)

Spinal muscular atrophy (SMA) is a genetic disease that attacks nerve cells, called motor neurons, in your spinal cord. These neurons communicate with your voluntary muscles - the ones you can control, like in your arms and legs. As you lose the neurons, your muscles weaken. This can affect walking, crawling, breathing, swallowing and head and neck control.

SMA runs in families. Parents usually have no symptoms, but still carry the gene. Genetic counseling is important if the disease runs in your family. There are many types of SMA, and some of them are fatal. Life expectancy depends on the type you have and how it affects your breathing. There is no cure. Medicines and physical therapy help treat symptoms.

BATTEN DISEASE

Batten disease is a fatal, inherited disorder of the nervous system that begins in childhood. In some cases, the early signs are subtle, taking the form of personality and behavior changes, slow learning, clumsiness, or stumbling. Symptoms of Batten disease are linked to a buildup of substances called lipopigments in the body's tissues.

Lipopigments are made up of fats and proteins. Because vision loss is often an early sign, Batten disease may be first suspected during an eye exam. Often, an eye specialist or other physician may refer the child to a neurologist. Diagnostic tests for Batten disease include blood or urine tests, skin or tissue sampling, an electroencephalogram (EEG), electrical studies of the eyes, and brain scans.

CANAVAN DISEASE

Canavan disease, one of the most common cerebral degenerative diseases of infancy, is a gene-linked, neurological birth disorder in which the brain degenerates into spongy tissue riddled with microscopic fluid-filled spaces. Canavan disease has been classified as one of a group of genetic disorders known as the leukodystrophies but unlike most leukodystrophies

both grey and white matter are severely affected in infants with Canavan disease. Recent research has indicated that the cells in the brain responsible for making myelin sheaths, known as oligodendrocytes, cannot properly complete this critical developmental task. Myelin sheaths are the fatty covering that act as insulators around nerve fibers in the brain, as well as providing nutritional support for nerve cells. In Canavan disease, many oligodendrocytes do not mature and instead die, leaving nerve cell projections known as axons vulnerable and unable to properly function. Canavan disease is caused by mutation in the gene for an enzyme called aspartoacylase, which acts to break down the concentrated brain chemical known as N-acetyl-aspartate.

MUCOLIPIDOSIS TYPE IV

Mucolipidosis type IV is an inherited disorder characterized by delayed development and progressive vision loss. The severe form of the disorder is called typical mucolipidosis type IV, and the mild form is called atypical mucolipidosis type IV.

People with typical mucolipidosis type IV have delayed development of mental and motor skills (psychomotor delay). Motor skills including sitting, standing, walking, grasping objects, and writing.Affected individuals have intellectual disability, limited or absent speech, difficulty chewing and swallowing, weak muscle tone (hypotonia) that gradually turns into abnormal muscle stiffness (spasticity), and problems controlling hand movements. Most people with typical mucolipidosis type IV are unable to walk independently. Vision may be normal at birth in people with typical mucolipidosis type IV, but it becomes increasingly impaired during the first decade of life. Individuals with this condition develop clouding of the clear covering of the eye (cornea) and progressive breakdown of the light-sensitive layer at the back of the eye (retina). By their early teens, affected individuals have severe vision loss or blindness.

NIEMANN-PICK DISEASE

Niemann-Pick disease (NP) refers to a group of inherited metabolic disorders known as lipid storage diseases. Lipids (fatty materials such as waxes, fatty acids, oils, and cholesterol) and proteins are usually broken down into smaller components to provide energy for the body. In Niemann-Pick disease, harmful quantities of lipids accumulate in the spleen, liver, lungs, bone marrow, and the brain. Symptoms may include lack of muscle coordination, brain degeneration, eye paralysis and an enlarged liver and spleen.

The disease has 4 related types. Type A, the most severe form, occurs in early infancy. It is characterized by an enlarged liver and spleen, and profound brain damage by six months of age. Children with this type rarely live beyond 18 months. Type B involves an enlarged liver and spleen, which usually occurs in the pre-teen years. The brain is not affected. In types A and B, insufficient activity of an enzyme called sphingomyelinase that causes the build up of toxic amounts of sphingomyelin, a fatty substance present in every cell of the body. Types C and D may appear early in life or develop in the teen or adult years. Affected individuals have only moderate enlargement of the spleen and liver, difficulty in walking and swallowing, and progressive loss of vision and hearing. Types C and D are characterized by a defect that disrupts the transport of cholesterol between brain cells.

SALLA DISEASE

Salla disease and infantile sialic acid storage disorder are autosomal recessive disorders caused by mutations of the gene, which encodes a lysosomal membrane transporter. Neuromuscular symptoms dominate the clinical picture.

PROGRESSIVE SUPRANUCLEAR PLASY

Progressive supranuclear palsy (PSP) is a rare brain disorder that causes serious and progressive problems with control of gait and balance, along with complex eye movement and thinking problems. One of the classic signs of the disease is an inability to aim the eyes properly, which occurs because of lesions in the area of the brain that coordinates eye movements.

The disorder's long name indicates that the disease begins slowly and continues to get worse (progressive), and causes weakness (palsy) by damaging certain parts of the brain above pea-sized structures called nuclei that control eye movements (supranuclear).

SCHIZOPHRENIA

Schizophrenia is a chronic, severe, debilitating mental illness that affects about 1% of the population, more than 2 million people in the United States alone.With the sudden onset of severe psychotic symptoms, the individual is said to be experiencing acute schizophrenia. Psychotic means out of touch with reality or unable to separate real from unreal experiences.

There is no known single cause of schizophrenia. As discussed later, it appears that genetic factors produce a vulnerability to schizophrenia, with environmental factors contributing to different degrees in different individuals. There are a number of various treatments for schizophrenia. Given the complexity of schizophrenia, the major questions about this disorder (its cause or causes, prevention, and treatment) are unlikely to be resolved in the near future. The public should beware of those offering "the cure" for (or "the cause" of) schizophrenia.

LYME DISEASE

Lyme disease is caused by the bacterium Borrelia burgdorferi and is transmitted to humans through the bite of infected blacklegged ticks. Typical symptoms include fever, headache, fatigue, and a characteristic skin rash called Erythema migrans. If left untreated, infection can spread to joints, the heart, and the nervous system.

Lyme disease is diagnosed based on symptoms, physical findings (e.g., rash), and the possibility of exposure to infected ticks; laboratory testing is helpful if used correctly and performed with validated methods. Most cases of Lyme disease can be treated successfully with a few weeks of antibiotics.

FATAL FAMILIAL INSOMNIA

Fatal familial insomnia (FFI) begins as an unexplained inability to sleep during middle age and rapidly degrades into a fatal insomnia. Apparently, it is caused by a genetic mutation which subsequently leads to a prion disease, most probably related in nature to the Mad Cow Disease and Kuru (the genetic laughing disease usually found in cannibalistic tribes that lived in New Guinea) and even Alzheimer's Disease.

TAY-SACHS DISEASE

Infants with Tay-Sachs disease appear to develop normally for the first few months of life. Then, as nerve cells become distended with fatty material, a relentless deterioration of mental and physical abilities occurs. The child becomes blind, deaf, and unable to swallow. Muscles begin to atrophy and paralysis sets in.

Other neurological symptoms include dementia, seizures, and an increased startle reflex to noise. A much rarer form of the disorder occurs in patients in their twenties and

early thirties and is characterized by an unsteady gait and progressive neurological deterioration. Persons with Tay-Sachs also have "cherry-red" spots in their eyes.

The incidence of Tay-Sachs is particularly high among people of Eastern European and Askhenazi Jewish descent. Patients and carriers of Tay-Sachs disease can be identified by a simple blood test that measures beta-hexosaminidase A activity. Both parents must carry the mutated gene in order to have an affected child. In these instances, there is a 25 percent chance with each pregnancy that the child will be affected with Tay-Sachs disease. Prenatal diagnosis is available if desired.

NEUROCANTHOCYTOSIS

Neuroacanthocytosis refers to a group of genetic conditions that are characterized by movement disorders and acanthocytosis (abnormal, spiculated red blood cells).

Four syndromes are classified as neuroacanthocytosis: Chorea-acanthocytosis, McLeod syndrome, Huntington's disease-like 2 (HDL2), and panthothenate kinase-associated neurodegeneration (PKAN). A canthocytosis may not always be observed in HDL2 and PKAN. These disorders are caused by different genetic mutations, and the signs and symptoms vary, but usually include chorea (involuntary, dance-like movements), parkinsonism (slowness of movement), dystonia (abnormal body postures), and problems walking.

There may also be muscle weakness, involuntary movements of the face and tongue, tongue/lip biting (which is mostly characteristic of Chorea-acanthocytosis), as well as difficulty with speech and eating, cognitive impairment, psychiatric symptoms, and seizures.

Individuals with McLeod syndrome often have cardiac problems. Many features of these disorders are due to degeneration of the basal ganglia, a part of the brain that controls movement. Additional disorders that are also known have neurologic symptoms, acanthocytosis, and either lipoprotein disorders or systemic findings.

The diagnosis of neuroacanthocytosis is typically based on the symptoms and clinical observation, a review of family history, and the evaluation of specific laboratory and imaging studies.

SANDHOFF DISEASE

Sandhoff disease is a rare, genetic, lipid storage disorder resulting in the progressive deterioration of the central nervous system. It is caused by a deficiency of the enzyme beta-hexosaminidase, which results in the accumulation of certain fats (lipids) in the brain and other organs of the body. Sandhoff disease is a severe form of Tay-Sachs disease which is prevalent primarily in people of Eastern European and Ashkenazi Jewish descent but it is not limited to any ethnic group.

Onset of the disorder usually occurs at 6 months of age. Neurological symptoms may include motor weakness, startle reaction to sound, early blindness, progressive mental and motor deterioration, macrocephaly (an abnormally enlarged head), cherry-red spots in the eyes, seizures, and myoclonus (shock-like contractions of a muscle).

Other symptoms may include frequent respiratory infections, doll-like facial appearance, and an enlarged liver and spleen.

CHAPTER - 2
TOOLS AND TECHNIQUES

TOOLS USED:

2.1 Web Interface Building

2.2.1. HTML / CSS

HTML, which stands for Hyper Text Markup Language, is the predominant markup language for web pages. HTML is the basic building-blocks of web pages. Web browsers can also refer to Cascading Style Sheets (CSS) to define the appearance and layout of text and other material. CSS is designed primarily to enable the separation of document content (written in HTML or a similar markup language) from document presentation, including elements such as the layout, colors and fonts.

2.2.2 Adobe Dreamweaver (Vesrsion CS3) :

Adobe Dreamweaver (formerly Macromedia Dreamweaver) is propriety web development application originally created by Macromedia, and is now developed by Adobe Systems, which acquired Macromedia in 2005.

Dreamweaver is available for both Mac and Windows operating systems. Recent versions have incorporated support for web technologies such as CSS, JavaScript, and various server-side scripting languages and framework including ASP, ColdFusion, and PHP.

Features:

Adobe Dreamweaver is a proprietary web authoring application that provides synchronization features, the ability to find and replace lines of text or code by search terms and regular expressions across the entire site, and a templating feature that allows single-source update of shared code and layout across entire sites without scripting.

Dreamweaver is a professional HTML editor for designing, coding and developing websites, web pages and web applications. Whether you enjoy the control of hand-coding HTML/prefer to work in a visual editing environment, dreamweaver provides you with helpful to enhance your web creation experience.

Dreamweaver, like other HTML editors, edits files locally then uploads them to the remote web server using FTP, SFTP, or WebDAV. Dreamweaver CS4 now supports the Subversion (SVN) version control system.

To Create A Static Website:

1) Plan and prepare Create pages
2) Lay out and set up pages
3) Add content to your pages
4) Link pages together
5) Publish your site

2.2 WAMP Sever(Version 2.2.21)

WAMP is an acronym formed from the initials of the operating system Microsoft Windows and the principal components of the package: Apache, My SQL and one of PHP, Perl or Python. Apache is a web server. My SQL is an open-source database. PHP is a scripting language that can manipulate information held in a database and generate web pages dynamically each time content is requested by a browser.

2.3.1.Apache Server(Version 2.2)

Apache, is an established standard in the online distribution of website services, which gave the initial boost for the expansion of the World Wide Web. It is an open-source web server platform, which guarantees the online availability of the majority of the websites active today. The server is aimed at serving a great deal of widely popular modern web platforms/operating systems such as Unix, Windows, Linux, Solaris, Novell NetWare, FreeBSD, Mac OS X, Microsoft Windows, OS/2, etc.

2.3.2. My SQL(5.5.16)

My SQL is the world's most used relational database management system (RDBMS) that runs as a server providing multi-user access to a number of databases. The SQL phrase stands for Structured Query Language.

The My SQL development project has made its source code available under the terms of the GNU General Public License, as well as under a variety of proprietary agreements. Free-software-open source projects that require a full-featured database management system often use My SQL. For commercial use, several paid editions are available, and offer additional functionality.

2.3.3. PHP(Version 5.3.8)

PHP is a general-purpose server-side scripting language originally designed for Web development to produce dynamic Web pages. It is one of the first developed server-side scripting languages to be embedded into an HTML source document, rather than calling an external file to process data. Ultimately, the code is interpreted by a Web server with a PHP processor module which generates the resulting Web page.

It also has evolved to include a command-line interface capability and can be used in standalone graphical applications. PHP can be deployed on most Web servers and also as a standalone shell on almost every operating system and platform free of charge. A competitor to Microsoft's Active Server Pages (ASP) server-side script engine and similar languages, PHP is installed on more than 20 million Web sites and 1 million Web servers.

CHAPTER – 3
WORK DONE & METHODOLOGY

- Disease collection and selection
- Collection of basic information for diseases
- Collection of marker genes and their relevant information for all diseases
- Preparing csv (comma separated values) files for marker information and basic information of diseases
- Designing of an efficient GUI
- Designing and development of database

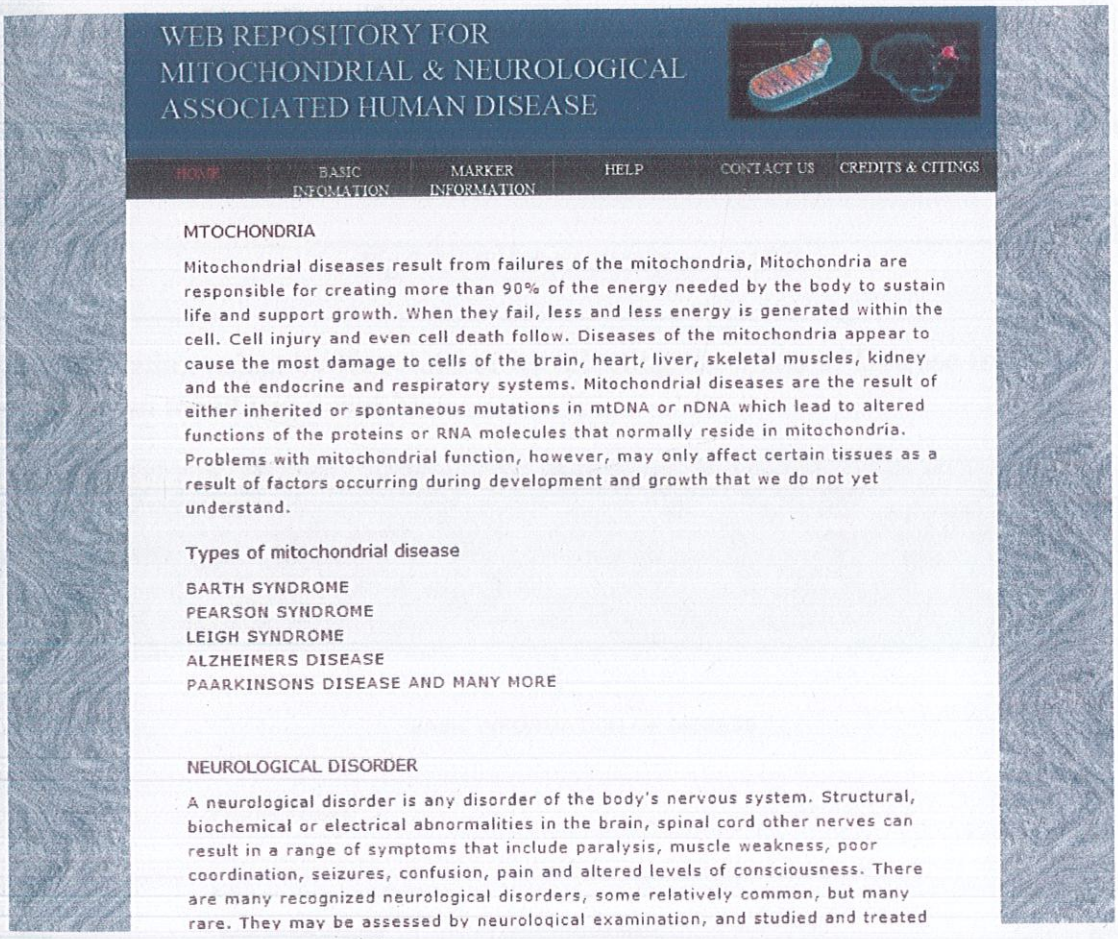


Fig.2. Home page of GUI with all options available in screenshot.

Basic information of disease:

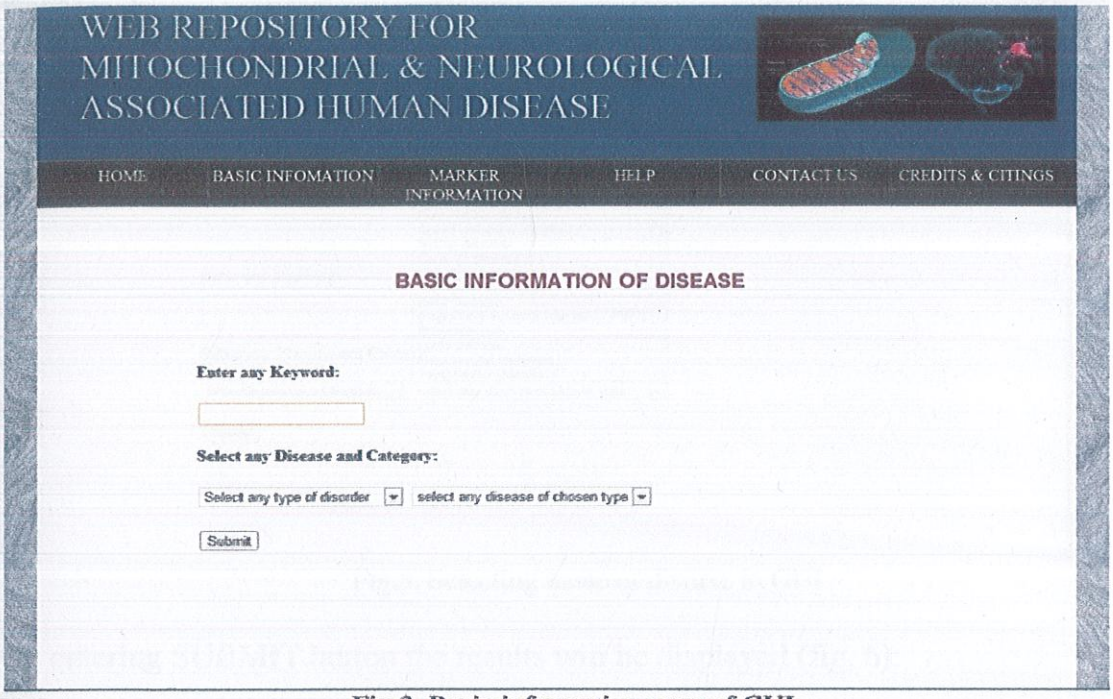


Fig.3. Basic information page of GUI

We can either select by Keyword or by selecting the name of Disease from the drop down menu (fig.4 and 5):

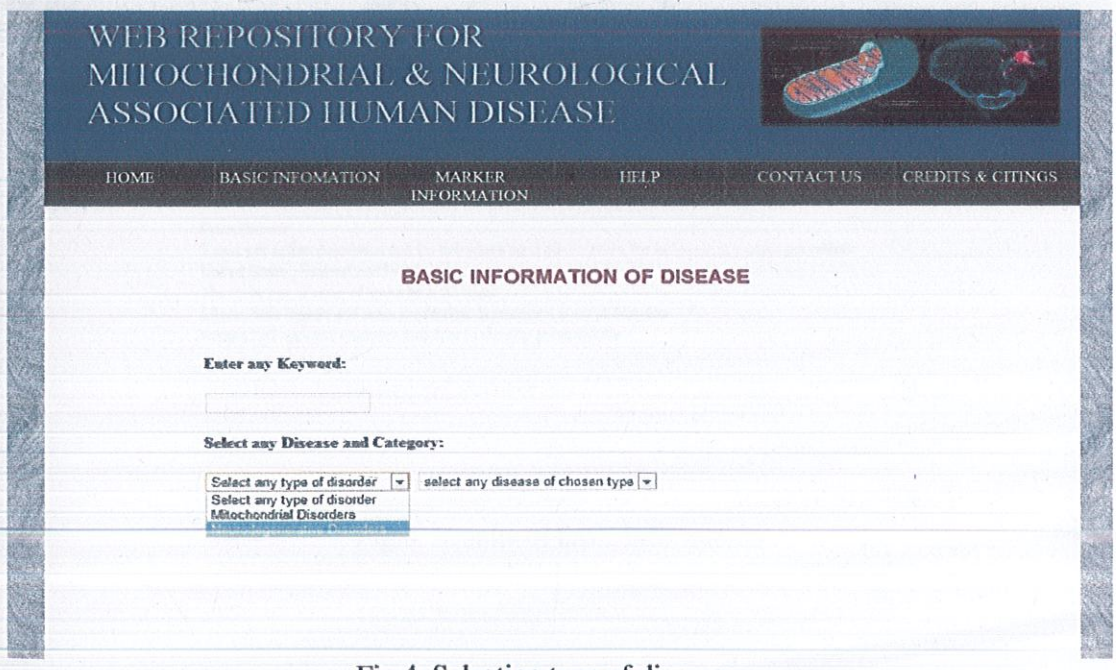


Fig.4. Selecting type of disease

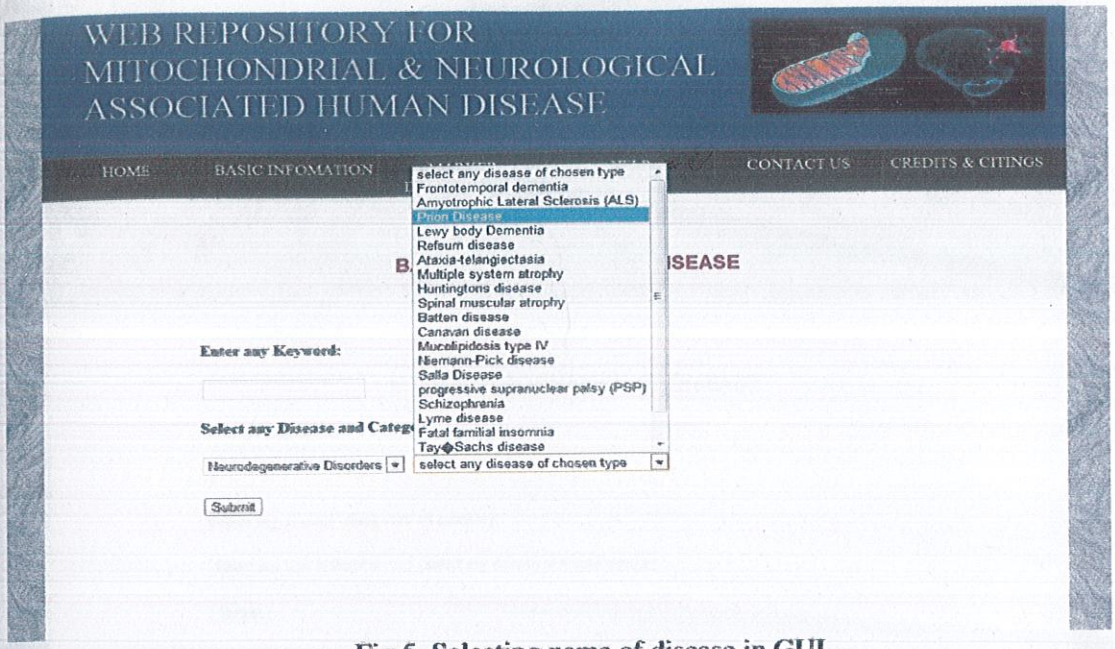


Fig.5. Selecting name of disease in GUI

On entering SUBMIT button the results will be displayed (fig. 6):

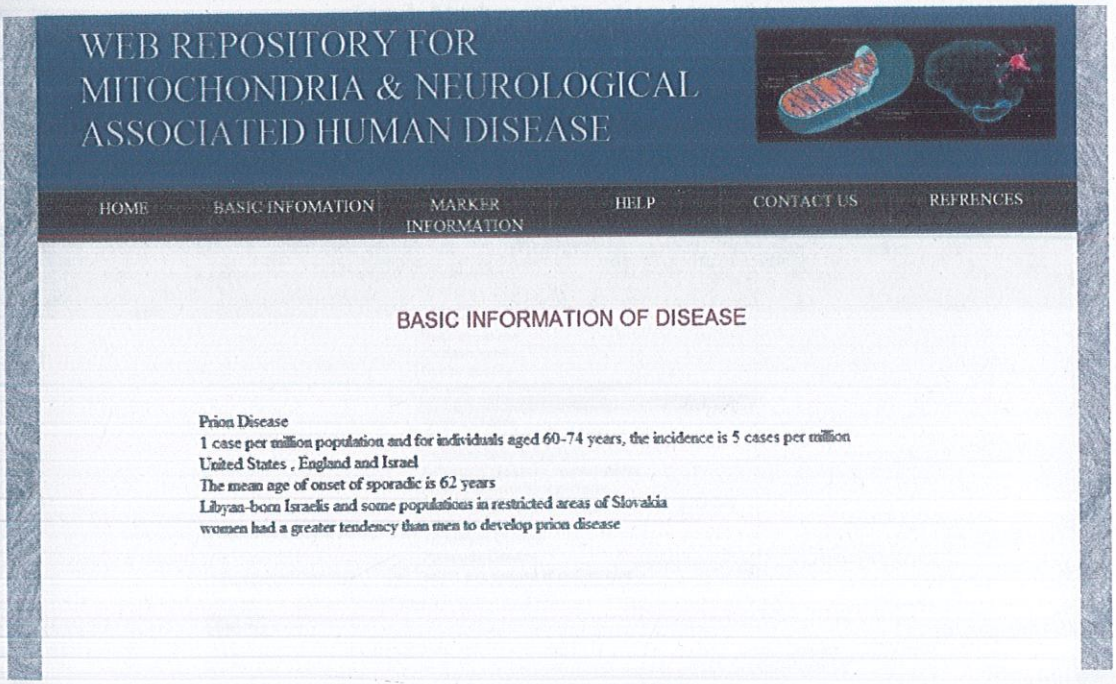


Fig.6. Results of basic information

Marker information associated with respective disease: All options will work like basic information (fig. 7-9). Results will be displayed in tabular format (fig. 10).

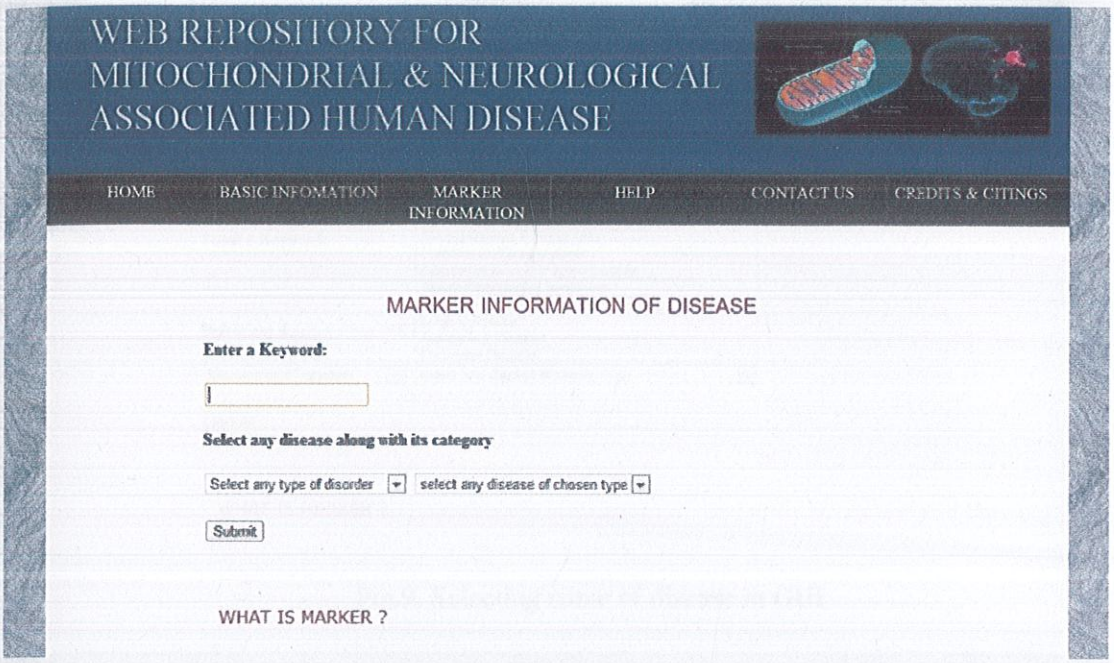


Fig.7. Marker information page of GUI

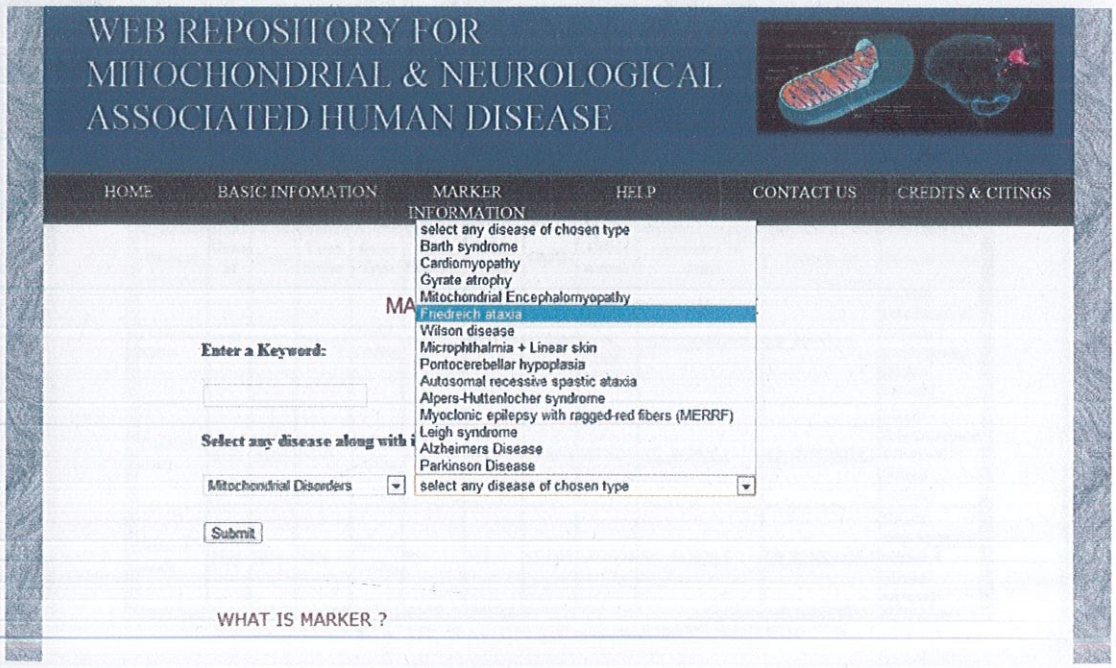


Fig.8. Selecting type of disease

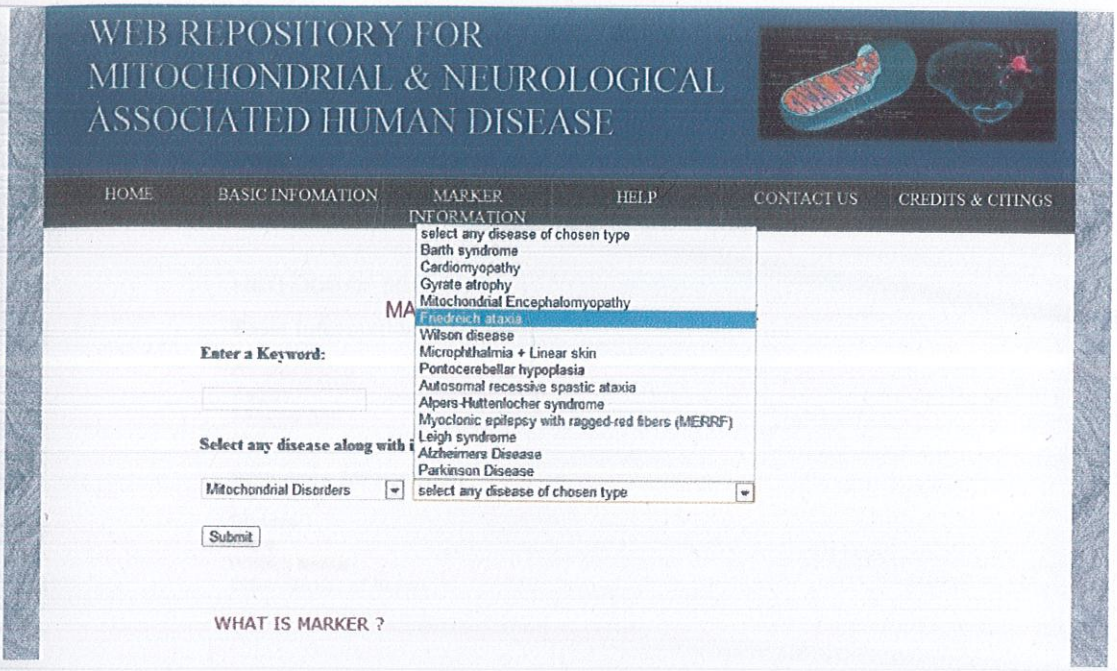
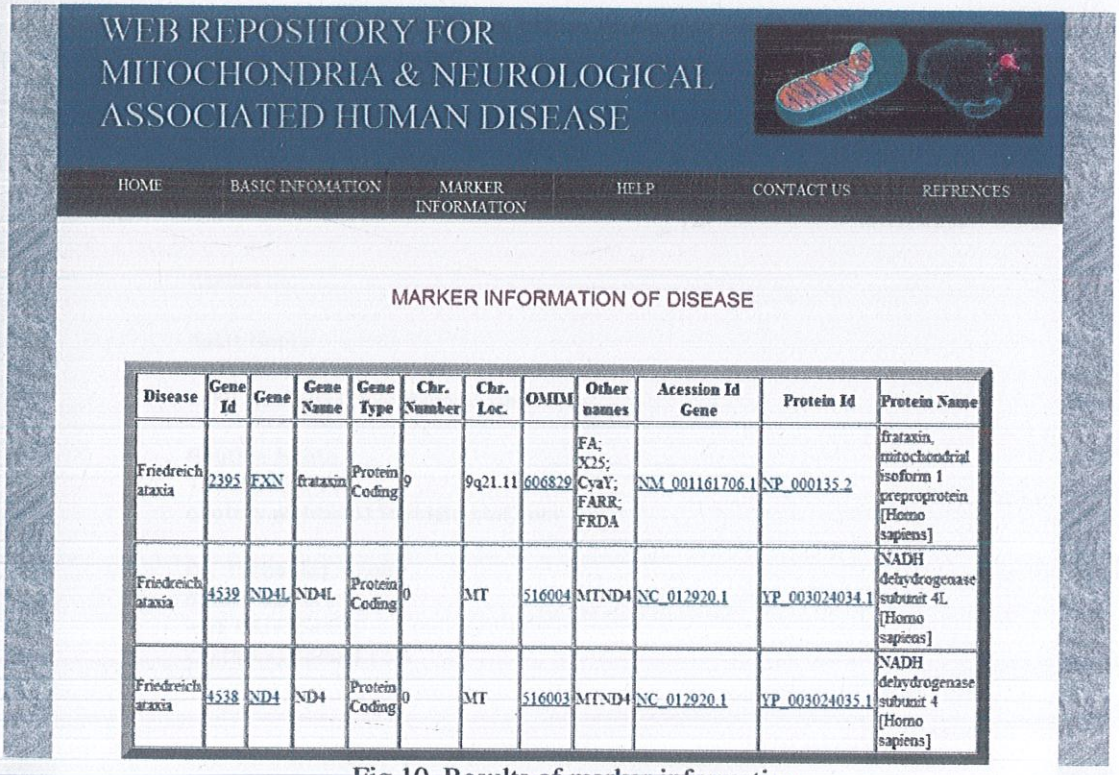


Fig.9. Selecting name of disease in GUI



Disease	Gene Id	Gene	Gene Name	Gene Type	Chr. Number	Chr. Loc.	OMIM	Other names	Acession Id Gene	Protein Id	Protein Name
Friedreich ataxia	2395	FXN	frataxin	Protein Coding	9	9q21.11	606829	FA; X25; CyaY; FARR; FRDA	NM_001161706.1	NP_000135.2	frataxin, mitochondrial isoform 1 preproprotein [Homo sapiens]
Friedreich ataxia	4539	ND4L	ND4L	Protein Coding	0	MT	516004	MTND4	NC_012920.1	YP_003024034.1	NADH dehydrogenase subunit 4L [Homo sapiens]
Friedreich ataxia	4538	ND4	ND4	Protein Coding	0	MT	516003	MTND4	NC_012920.1	YP_003024035.1	NADH dehydrogenase subunit 4 [Homo sapiens]

Fig.10. Results of marker information

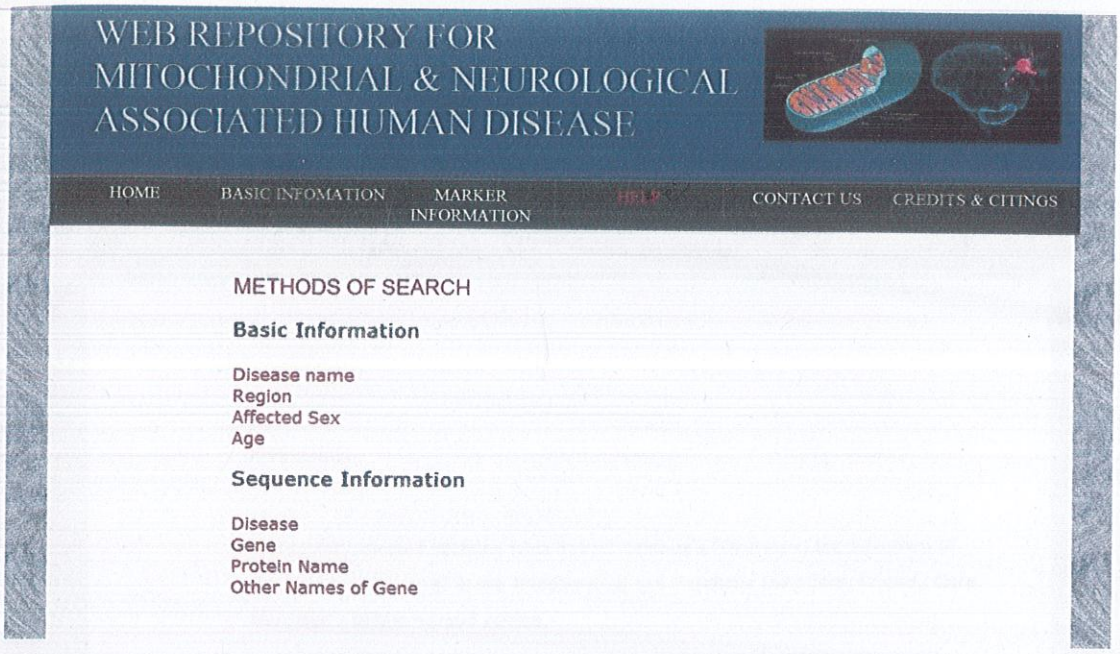


Fig.11. Help page in GUI

Fig.12. Contact page in GUI

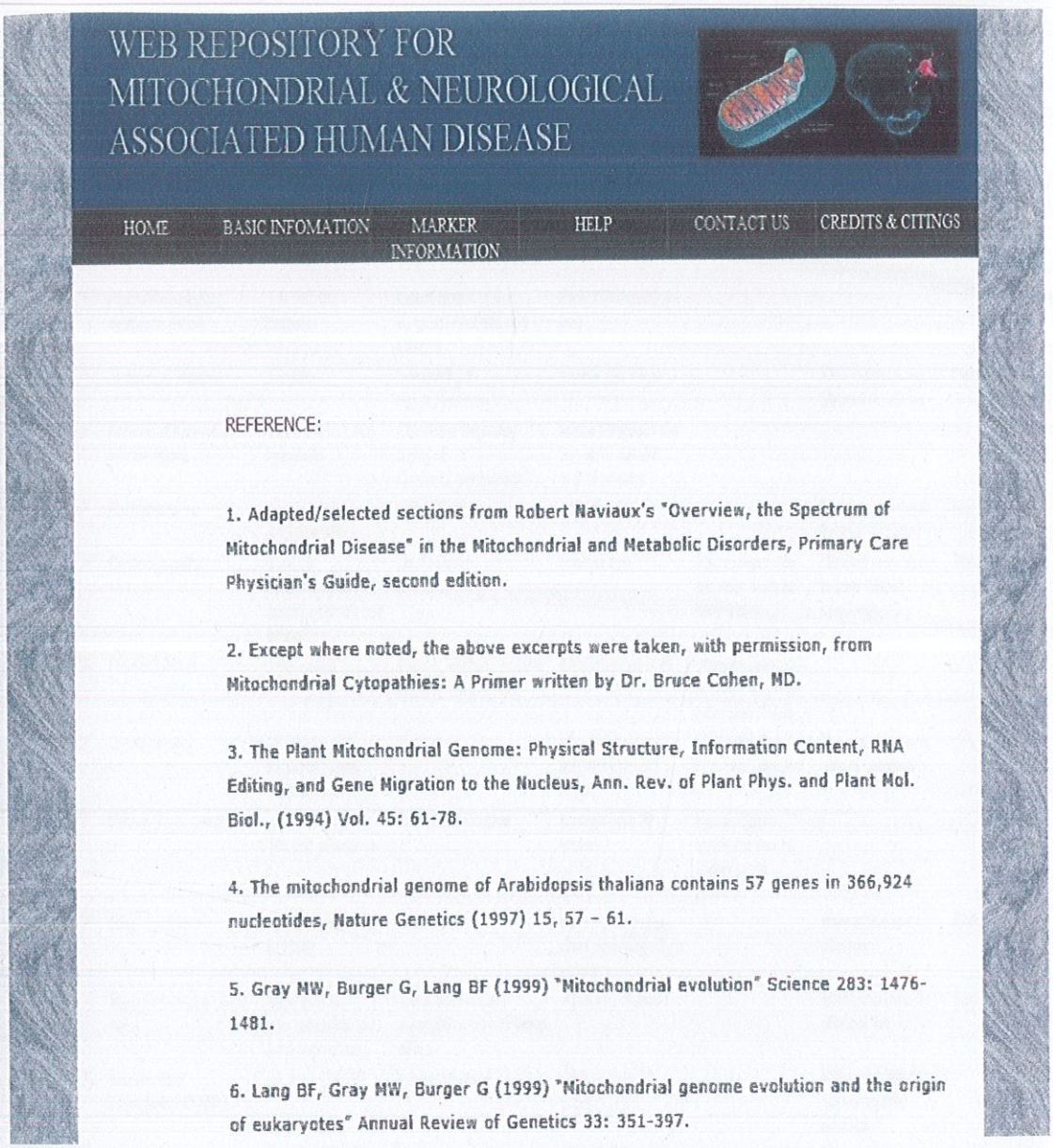


Fig.13. Credits and citing page in GUI

About The Background Database:

We have designed a table that depicts the occurrence, region, religion, affected sex, age of Mitochondrial associated human disease (fig. 14).

Alpers-Huttenlocher syndrome (AHS)	1 in 100,000 persons	United States United Kingdom Australia and Canada	Early Childhood(2-4 yrs)			
Alzheimers Disease	4 million	Industrialized region,America	mostly after 65yrs		More womans are affected than men	Female
Autosomal recessive spastic ataxia	1 in 1,500 to 2,000 individuals	Charlevoix-Saguenay region of Quebec,Canada,Japan,T...	appears between the age of 12 months and 18 months			
Barth syndrome	1 in 3,00,00-4,00,000(10/yr)	United States	early childhood		Males are affected (mother to son)	Male
Cardiomyopathy	1 in 500 fixhypertrophic cardiomyopathy and betwee...	UK Australia	younger age	African Americans are more likely to have dilated ...	Men are more likely to have dilated cardiomyopathy...	Male
Friedrich Ataxia	1 per 29000	Europe; North Americans of European descent	before the age of 20	common European ancestor who lived more than 10000...		
Gyrate atrophy	More than 150 individuals have been identified	Finland	inherited,symtoms from the chilhood stage.	Finish people are very much affected.	The male-to-female ratio is unknown	
Kearns-Sayre syndrome	1.17 cases per 100,000 population	North East England	younger than 20 years.	Kearns-Sayre syndrome has no known racial predilec...		
Leigh syndrome	less than 2,00,000(1 in 2000)	United States	betweeen 3 mnths -2yrs,next stage 2yrs -10yrs		more males are affected	Male
Microphthalmia + Linear skin	More than 50 affected individuals have been identi...	The prevalence of microphthalmia with linear skin ...	infant and chilhood		females are mostly affected than males	Females
Mitochondrial Encephalopathy(MELAS)	16.3 per 100,000	northern Finland	younger than 50 years		Males and females appear equally affected	
Myoclonic epilepsy and ragged-red fibers (MERRF)	1/400,000	Europe	Early Childhood(2-4 yrs)		Males and females appear equally affected	
Parkinson Disease	6.3 million &50,000 anually	nebraska,United States	average age 60yrs	highest among whites,in India Parsis	More man are affected	Male
Ponto-Cerebellar hypoplasia	3-5 cases per 100,000	United States	The mean age of onset of sporadic	No apparent racial preference in	a male-to-female ratio of 2:1	Male

Fig.14. Database of basic information of Mitochondrial Disease

We have designed a table that depicts the occurrence, region, religion, affected sex, age of Neurological associated human disease (fig. 15).

diseases	population	region	age	race	ratio	Affected_sex
Amyotrophic Lateral Sclerosis (ALS)	7 cases per 100,000	European,Finland and United States	Onset of ALS may occur from the teenage years to t...		The incidence of ALS is higher in men than in wome...	Male
Ataxia-telangiectasia	1 case in 100,000 births		early childhood	Ataxia-telangiectasia is reported in all races, al...	Ataxia-telangiectasia occurs equally among males a...	
Batten disease	2 to 4 of every 100,000	Finland, Sweden, other parts of northern Europe, a...	childhood	Only childs are affected.		
Canavan disease	1 in 6,400 to 13,500	eastern and central European	childhood	Most common in Ashkenazi Jewish heritage		
Fatal familial insomnia	1 case per million population and for individuals ...	United States , England and Israel	The age of onset is variable, ranging from 18 to 6...			
Frontotemporal dementia	5 cases per million and Among those aged 60-70 yea...	United States and England	typically between the ages of 40 and 70.		66% males and 34% females are affected.	Male
Huntingtons disease		Europe(Caussian people),Asia and Africa	middle-age	Caucasian people are very much affected generally ...	Huntingtons disease (HD) affects both men and wome...	
Lewy body Dementia	112 cases per 100,000 person-years in France	Asia Africa and Europe	late middle age and old age	Asian, African, and European races	Lewy body Dementia is slightly more common in men ...	Male
Lyme disease	9.1 cases per 100,000 persons	North America, Europe, and Asia	not known	Lyme disease is reported primarily in white indivi...	No report	
Mucolipidosis type IV	1 in 40,000	eastern and central European	childhood	About 70 % Ashkenazi Jewish heritage		
Multiple system atrophy	1.9-4.9 cases per 100,000 in	Africa Asia and some parts of Europe(Caucasian pop...	The mean age at onset in MSA	MSA has been encountered in	Female-to-male ratio is around	Male

Fig.15. Database of basic information of Neurological Disease

We have designed a table that depicts the Gene id, gene name, gene type, chromosome number, chromosome location, OMIM number, gene and protein link of Mitochondrial associated human disease (fig. 16).

Srno	disease	GeneId	gene	gene_name	gene_type	chromosomeno	chromosome_location	OMIM	gene_link
1	Cardiomyopathy	4508	ATP6	ATP synthase F0 subunit 6	Protein Coding	0	MT	516060	http://www.ncbi.nlm.nih.gov/
2	Barth Syndrome	6901	TAZ	tafazzin	Protein Coding	23	Xq28	300394	http://www.ncbi.nlm.nih.gov/
3	Cardiomyopathy	4509	ATP8	ATP synthase F0 subunit 8	Protein Coding	0	MT	516070	http://www.ncbi.nlm.nih.gov/
4	Cardiomyopathy	7137	TNNI3	troponin I type 3 (cardiac)	Protein Coding	19	19q13.4	191044	http://www.ncbi.nlm.nih.gov/
5	Mitochondrial Encephalomyopathy	4535	MT-ND1	MT-ND1	Protein Coding	0	MT	516000	http://www.ncbi.nlm.nih.gov/
6	Mitochondrial Encephalomyopathy	4540	MT-ND5	MT-ND5	Protein Coding	0	MT	516005	http://www.ncbi.nlm.nih.gov/
7	Mitochondrial Encephalomyopathy	4564	MT-TH	MTTH	tRNA	0	MT	590040	http://www.ncbi.nlm.nih.gov/
8	Mitochondrial Encephalomyopathy	4567	MT-TL1	MT-TL1	tRNA	0	MT	590050	http://www.ncbi.nlm.nih.gov/
9	Mitochondrial Encephalomyopathy	4577	MT-TV	MT-TV	tRNA	0	MT	590105	http://www.ncbi.nlm.nih.gov/
10	Mitochondrial Encephalomyopathy	4519	CYTB	CYTB	Protein Coding	0	MT	516020	http://www.ncbi.nlm.nih.gov/
11	Friedreich ataxia	2395	FXN	frataxin	Protein	9	9q21.11	606829	http://www.ncbi.nlm.nih.gov/

Fig.16. Database of Marker information of Mitochondrial Disease

We have designed a table that depicts the Gene id, gene name, gene type, chromosome number, chromosome location, OMIM number, gene and protein link of mitochondrial associated human disease (fig. 17).

Srno	disease	Geneid	gene	gene_name	gene_type	chromosomeno	chromosome_location	OMIM	gene_link
1	Frontotemporal dementia	2896	GRN	granulin	Protein Coding	17	17q21.32	138945	http://www.ncbi.nlm.nih.g
2	Frontotemporal dementia	7415	VCP	valosin containing protein	Protein Coding	9	9p13.3	601023	http://www.ncbi.nlm.nih.g
3	Frontotemporal dementia	23435	TARDBP	TAR DNA binding protein	Protein Coding	1	1p36.22	605078	http://www.ncbi.nlm.nih.g
4	Frontotemporal dementia	203228	C9ORF72	chromosome 9 open reading frame 72	Protein Coding	9	9p21.2	614260	http://www.ncbi.nlm.nih.g
5	Amyotrophic Lateral Sclerosis (ALS)	6647	SOD1	superoxide dismutase 1 soluble	Protein Coding	21	21q22.1; 21q22.11	147450	http://www.ncbi.nlm.nih.g
6	Amyotrophic Lateral Sclerosis (ALS)	57679	ALS2	amyotrophic lateral sclerosis 2 (juvenile)	Protein Coding	2	2q33.1	606352	http://www.ncbi.nlm.nih.g
7	Amyotrophic Lateral Sclerosis (ALS)	23064	SETX	senataxin	Protein Coding	9	9q34.13	608465	http://www.ncbi.nlm.nih.g
8	Amyotrophic Lateral Sclerosis (ALS)	2521	FUS	fused in sarcoma	Protein Coding	16	16p11.2	137070	http://www.ncbi.nlm.nih.g
9	Amyotrophic Lateral Sclerosis (ALS)	9217	VAPB	VAMP (vesicle-associated membrane protein)-associa	Protein Coding	20	20q13.33	605704	http://www.ncbi.nlm.nih.g

Fig.17.Database of basic information of Neurological Disease:

3.1 Structure of tables in Database

Browse | Structure | SQL | Search | Insert | Export | Import | Operations | Empty | Drop

	Field	Type	Collation	Attributes	Null	Default	Extra	Action
☐	diseases	varchar(100)	latin1_swedish_ci		No	None		
☐	population	varchar(300)	latin1_swedish_ci		Yes	NULL		
☐	region	varchar(1000)	latin1_swedish_ci		Yes	NULL		
☐	age	varchar(100)	latin1_swedish_ci		Yes	NULL		
☐	race	varchar(1000)	latin1_swedish_ci		Yes	NULL		
☐	ratio	varchar(1000)	latin1_swedish_ci		Yes	NULL		
☐	Affected_sex	varchar(10)	latin1_swedish_ci		Yes	NULL		

Check All / Uncheck All *With selected:*

Print view | Relation view | Propose table structure

Add 1 field(s) ◉ At End of Table ○ At Beginning of Table ○ After diseases Go

Indexes:

Action	Keyname	Type	Unique	Packed	Field	Cardinality	Collation	Null	Comment
	PRIMARY	BTREE	Yes	No	diseases	15	A		

Create an index on 1 columns Go

+ Details...

Fig.18. Structure of Table basic information of Mitochondrial Disease

Browse | Structure | SQL | Search | Insert | Export | Import | Operations | Empty | Drop

	Field	Type	Collation	Attributes	Null	Default	Extra	Action
☐	diseases	varchar(100)	latin1_swedish_ci		No	None		
☐	population	varchar(300)	latin1_swedish_ci		Yes	NULL		
☐	region	varchar(1000)	latin1_swedish_ci		Yes	NULL		
☐	age	varchar(100)	latin1_swedish_ci		Yes	NULL		
☐	race	varchar(1000)	latin1_swedish_ci		Yes	NULL		
☐	ratio	varchar(1000)	latin1_swedish_ci		Yes	NULL		
☐	Affected_sex	varchar(10)	latin1_swedish_ci		Yes	NULL		

Check All / Uncheck All *With selected:*

Print view | Relation view | Propose table structure

Add 1 field(s) ◉ At End of Table ○ At Beginning of Table ○ After diseases Go

Indexes:

Action	Keyname	Type	Unique	Packed	Field	Cardinality	Collation	Null	Comment
	PRIMARY	BTREE	Yes	No	diseases	21	A		

Create an index on 1 columns Go

+ Details...

Fig.19. Structure of Table basic information of Neurological Disease:

Browse | Structure | SQL | Search | Insert | Export | Import | Operations | Empty | Drop

Field	Type	Collation	Attributes	Null	Default	Extra	Action
Smo	int(11)			No	None		
disease	varchar(200)	latin1_swedish_ci		Yes	NULL		
Geneid	double			Yes	NULL		
gene	varchar(20)	latin1_swedish_ci		Yes	NULL		
gene_name	varchar(100)	latin1_swedish_ci		Yes	NULL		
gene_type	varchar(50)	latin1_swedish_ci		Yes	NULL		
chromosomeno	int(11)			Yes	NULL		
chromosome_location	varchar(20)	latin1_swedish_ci		Yes	NULL		
OMIM	double			Yes	NULL		
gene_link	varchar(100)	latin1_swedish_ci		Yes	NULL		
other_names	varchar(300)	latin1_swedish_ci		Yes	NULL		
accessiong	varchar(100)	latin1_swedish_ci		Yes	NULL		
nlink	varchar(100)	latin1_swedish_ci		Yes	NULL		
plink	varchar(100)	latin1_swedish_ci		Yes	NULL		
proteinid	varchar(20)	latin1_swedish_ci		Yes	NULL		
pname	varchar(100)	latin1_swedish_ci		Yes	NULL		
OMIMlink	varchar(100)	latin1_swedish_ci		Yes	NULL		

Check All / Uncheck All *With selected:*

Print view | Relation view | Propose table structure

Add 1 field(s) At End of Table At Beginning of Table After Smo Go

Indexes:

Action	Keyname	Type	Unique	Packed	Field	Cardinality	Collation	Null	Comment
	PRIMARY	BTREE	Yes	No	Smo	76	A		

Create an index on 1 columns Go

Fig.20. Structure of Table marker information of Mitochondrial Disease

Browse Structure SQL Search Insert Export Import Operations Empty Drop

Field	Type	Collation	Attributes	Null	Default	Extra	Action
Smo	int(11)			No	None		
disease	varchar(100)	latin1_swedish_ci		Yes	NULL		
GeneId	double			Yes	NULL		
gene	varchar(20)	latin1_swedish_ci		Yes	NULL		
gene_name	varchar(100)	latin1_swedish_ci		Yes	NULL		
gene_type	varchar(50)	latin1_swedish_ci		Yes	NULL		
chromosomeno	int(11)			Yes	NULL		
chromosome_location	varchar(20)	latin1_swedish_ci		Yes	NULL		
OMIM	double			Yes	NULL		
gene_link	varchar(100)	latin1_swedish_ci		Yes	NULL		
other_names	varchar(300)	latin1_swedish_ci		Yes	NULL		
acessiong	varchar(400)	latin1_swedish_ci		Yes	NULL		
nlink	varchar(100)	latin1_swedish_ci		Yes	NULL		
plink	varchar(100)	latin1_swedish_ci		Yes	NULL		
proteinid	varchar(20)	latin1_swedish_ci		Yes	NULL		
pname	varchar(100)	latin1_swedish_ci		Yes	NULL		
OMIMlink	varchar(100)	latin1_swedish_ci		Yes	NULL		

Check All / Uncheck All With selected:

Print view Relation view Propose table structure

Add 1 field(s) At End of Table At Beginning of Table After Smo Go

Indexes:

Action	Keyname	Type	Unique	Packed	Field	Cardinality	Collation	Null	Comment
	PRIMARY	BTREE	Yes	No	Smo	61	A		

Create an index on 1 columns Go

Fig.21. Structure of Table marker information of Mitochondrial Disease

3.2 Codes Used In Developing Database and GUIs

Creation of empty database: database.php

```
<?php
$dbhost='localhost';
$dbuser='root';
$a=mysql_connect($dbhost,$dbuser);
if(!$a)
{
echo "connected sucessfully";
}
$sql=mysql_query('CREATE database ankit');
if(!$sql)
{
echo mysql_error();
}
?>
```

Basic Information

Creation of table for mitochondrial disease:mdtable.php

```
<?php
$dbhost='localhost';
$dbuser='root';
$a=mysql_connect($dbhost,$dbuser);
mysql_select_db('ankit');
$sql=mysql_query("CREATE table mitochondria(diseases varchar(100) PRIMARY KEY,
population varchar(300),
region varchar(1000),
age varchar(100),
race varchar(1000),
ratio varchar(1000),
```

```
Affected_sex varchar(10)

)");
if(!$sql)
{
echo mysql_error();
}
?>
```

Creation of table for neurodegenerative disorders: neurotable.php

```
<?php
$dbhost='localhost';
$dbuser='root';
$a=mysql_connect($dbhost,$dbuser);
mysql_select_db('ankit');
$sql=mysql_query("CREATE table brain(diseases varchar(100) PRIMARY KEY,
population varchar(300),
region varchar(1000),
age varchar(100),
race varchar(1000),
ratio varchar(1000),
Affected_sex varchar(10))");
if(!$sql)
{
echo mysql_error();
}
?>
```

Insertion of data to table “mitochondria”:insert.php

```
<?php
$dbhost='localhost';
$dbuser='root';
$a=mysql_connect($dbhost,$dbuser);
```

```
$a=fopen("Disease_chart.csv","r");
$b=fgets($a);
$d=explode(',',$b);
mysql_select_db('ankit');
while(($c = fgetcsv($a,100000000,','))!=FALSE)
{
$sql=mysql_query(" INSERT INTO
mitochondria(diseases,population,region,age,race,ratio,Affected_sex
)VALUES('$c[0]','$c[1]','$c[2]','$c[3]','$c[4]','$c[5]','$c[6]')");
}
if(!$sql)
{
echo mysql_error();
}
?>
```

Insertion of data to table "brain":neuroinsert.php

```
<?php
$dbhost='localhost';
$dbuser='root';
$a=mysql_connect($dbhost,$dbuser);
$a=fopen("neuro.csv","r");
$b=fgets($a);
$d=explode(',',$b);
mysql_select_db('ankit');
while(($c = fgetcsv($a,100000000,','))!=FALSE)
{
$sql=mysql_query(" INSERT INTO
brain(diseases,population,region,age,race,ratio,Affected_sex
)VALUES('$c[0]','$c[1]','$c[2]','$c[3]','$c[4]','$c[5]','$c[6]')");
}
if(!$sql)
```

```
{
echo mysql_error();
}
?>
```

Retrieving information from tables “mitochondria” and “brain” script :select.php

```
<!DOCTYPE html PUBLIC "-//W3C//DTD XHTML 1.0 Transitional//EN"
"http://www.w3.org/TR/xhtml1/DTD/xhtml1-transitional.dtd">
<html xmlns="http://www.w3.org/1999/xhtml">
<head>
<meta http-equiv="Content-Type" content="text/html; charset=utf-8" />
<title>Basic Information</title>
<link href="CSS/Stylesheet.css" type="text/css" rel="stylesheet" />
</head>

<body>
<div id="wrap">
<div id="header_cont">
<div id="logo_line">WEB REPOSITORY FOR MITOCHONDRIA & NEUROLOGICAL
ASSOCIATED HUMAN DISEASE</div>
<div id="logo_image"><img src="Images/header_image.jpg" /></div>
</div>
<div id="nav">
<div id="nav1"><a href="index.html">HOME</a></div>
<div id="nav1"><a href="basic info.html">BASIC INFOMATION</a></div>
<div id="nav1"><a href="marker info.html">MARKER INFORMATION </a></div>
<div id="nav1"><a href="help.html">HELP</a></div>
<div id="nav1"><a href="contact us.html">CONTACT US</a></div>
<div id="nav1"><a href="refrences.html">REFRENCES</a></div>
</div>
</div>
```

```
<div id="main_cont">
<div id="basic_main_cont">
<div id="basic">

<br>
<br>
<br>

<?php
error_reporting(0);
$z=$_POST['abc'];
$x=$_POST['cities'];?>
<b><font color="blue" size="6">You are Looking for:</b></font> <i><font color="red" size
= "6"><?php echo $row[1];?></font></i>

<?php
$dbhost='localhost';
$dbuser='root';
$a=mysql_connect($dbhost,$dbuser);
mysql_select_db('ankit');

?>
<br>
<br>
<br>
<?php
if($z == '' ){
?>
<script type="text/javascript">
alert("Please select any category")
</script>
<a href="basic info.html"><input type="button" value="back"></a>
<?php
break;
```

```
}
?>
<?php
if($z != " brain " )
{
$sql=mysql_query("SELECT * FROM  mitochondria  WHERE diseases = '$x' ");
}
if($z == "brain")
{
$sql=mysql_query("SELECT * FROM brain WHERE diseases = '$x' ");
}
if(mysql_num_rows($sql)>0)
{
while($row=mysql_fetch_row($sql))
{
print_r($row[0]);
echo "<br/>";
print_r($row[1]);
echo "<br/>";
print_r($row[2]);
echo "<br/>";
print_r($row[3]);
echo "<br/>";
print_r($row[4]);
echo "<br/>";
print_r($row[5]);
echo "<br/>";
echo "<br/>";
echo "<br/>";
}
}
?>
</div>
</div>
```

```
</div>
</body>
</html>
```

Marker Information

Creation of table "mdseq":mdseq.php

```
<?php
$dbhost='localhost';
$dbuser='root';
$a=mysql_connect($dbhost,$dbuser);
mysql_select_db('ankit');
$sql=mysql_query("CREATE table mdseq(Srno int PRIMARY KEY,
disease varchar(200),
Geneid double,
gene varchar(20),
gene_name varchar(100),
gene_type varchar(50),
chromosomeno int,
chromosome_location varchar(20),
OMIM double,
gene_link varchar(100),
other_names varchar(300),
acessiong varchar(100),
nlink varchar(100),
plink varchar(100),
proteinid varchar(20),
pname varchar(100),
OMIMlink varchar(100)
)");
if(!$sql)
{
echo mysql_error();
```

```
}
?>
```

Creation of table "brainseq":brainseq.php

```
<?php
$dbhost='localhost';
$dbuser='root';
$a=mysql_connect($dbhost,$dbuser);
mysql_select_db('ankit');
$sql=mysql_query("CREATE table brainseq(Srno int PRIMARY KEY,
disease varchar(100),
Geneid double,
gene varchar(20),
gene_name varchar(100),
gene_type varchar(50),
chromosomeno int,
chromosome_location varchar(20),
OMIM double,
gene_link varchar(100),
other_names varchar(300),
acessiong varchar(400),
nlink varchar(100),
plink varchar(100),
proteinid varchar(20),
pname varchar(100),
OMIMlink varchar(100)
)");
if(!$sql)
{
echo mysql_error();
}
?>
```

Insertion of data into table "mdseq":mtdinsert.php

```
<?php
$filename="C:\wamp\www\PROJECT\sequences\gne.csv";
$file=fopen($filename,"r");
$fi=fgets($file);
$f=explode(",",$fi);
$dbhost='localhost';
$dbuser='root';
$a=mysql_connect($dbhost,$dbuser);
mysql_select_db('ankit');
while(($data = fgetcsv($file,100000000,','))!=FALSE)
{
$sql=mysql_query("INSERT INTO mdseq(Srno,
disease,
Geneid,
gene,
gene_name,
gene_type,
chromosomeno,
chromosome_location,
OMIM,
gene_link,
other_names,
acessiong,
nlink ,
plink ,
proteinid ,
pname ,
OMIMlink
)VALUES('$data[0]','$data[1]','$data[2]','$data[3]','$data[4]','$data[5]','$data[6]','$data[7]','$d
ata[8]','$data[9]','$data[10]','$data[11]','$data[12]','$data[13]','$data[14]','$data[15]','$data[16]'
)");
}
```

```
if(!$sql)
{
echo mysql_error();
}
?>
```

Insertion of data into “brainseq”:braininsert.php

```
<?php
$filename="neuro.csv";
$file=fopen($filename,"r");
$fi= fgets($file);
$f=explode(",",$fi);
$dbhost='localhost';
$dbuser='root';
$a=mysql_connect($dbhost,$dbuser);
mysql_select_db('ankit');
while(($data = fgetcsv($file,100000000,',')) != FALSE)
{
$sql=mysql_query("INSERT INTO brainseq(Srno,
disease,
Geneid,
gene,
gene_name,
gene_type,
chromosomeno,
chromosome_location,
OMIM,
gene_link,
other_names,
acessiong,
nlink ,
plink ,
proteinid ,
```

```
pname ,
OMIMlink
)VALUES('$data[0]','$data[1]','$data[2]','$data[3]','$data[4]','$data[5]','$data[6]','$data[7]','$d
ata[8]','$data[9]','$data[10]','$data[11]','$data[12]','$data[13]','$data[14]','$data[15]','$data[16]'
)");
}
if(!$sql)
{
echo mysql_error();
}
?>
```

Retriving information from both the tables "mdseq" and "brainseq":selectseq.php

```
<!DOCTYPE html PUBLIC "-//W3C//DTD XHTML 1.0 Transitional//EN"
"http://www.w3.org/TR/xhtml1/DTD/xhtml1-transitional.dtd">
<html xmlns="http://www.w3.org/1999/xhtml">
<head>
<meta http-equiv="Content-Type" content="text/html; charset=utf-8" />
<title>Basic Information</title>
<link href="CSS/Stylesheet.css" type="text/css" rel="stylesheet" />
</head>

<body>
<div id="wrap">
<div id="header_cont">
<div id="logo_line">WEB REPOSITORY FOR MITOCHONDRIA & NEUROLOGICAL
ASSOCIATED HUMAN DISEASE</div>
<div id="logo_image"><img src="Images/header_image.jpg" /></div>
</div>

<div id="nav">
<div id="nav1"><a href="index.html">HOME</a></div>
<div id="nav1"><a href="basic info.html">BASIC INFOMATION</a></div>
```

```
<div id="nav1"><a href="marker info.html">MARKER INFORMATION </a></div>
<div id="nav1"><a href="help.html">HELP</a></div>
<div id="nav1"><a href="contact us.html">CONTACT US</a></div>
<div id="nav1"><a href="refrences.html">REFRENCES</a></div>

</div>
<div id="main_cont">
<div id="basic_main_cont">
<div id="basic">
<h1><center>MARKER INFORMATION OF DISEASE</center></h1>
</div>
<?php
error_reporting(0);
$dbhost='localhost';
$dbuser='root';
$a=mysql_connect($dbhost,$dbuser);
mysql_select_db('ankit');
$d=$_POST['b'];
$c=$_POST['cities'];
$e=$_POST['t'];
if($d != "brainseq")
{
$sql=mysql_query("SELECT * FROM mdseq WHERE disease ='$c'");
}
if($d == "brainseq")
{
$sql=mysql_query("SELECT * FROM brainseq WHERE disease = '$c'");
}
if(($d == "") && ($c == ""))
{
$sql=mysql_query("SELECT * FROM brainseq WHERE disease LIKE '$e%' OR disease
LIKE '%$e' OR disease LIKE '%$e%' OR gene LIKE '$e%' OR gene LIKE '%$e' OR gene
LIKE '%$e%' OR pname LIKE '$e%' OR pname  LIKE '%$e'  OR pname LIKE '%$e%' OR
other_names LIKE '$e%' OR other_names LIKE '%$e' OR other_names LIKE '%$e%'
```

```
UNION SELECT * FROM mdseq WHERE disease LIKE '$e%' OR disease LIKE '%$e' OR
disease LIKE '%$e%' OR gene LIKE '$e%' OR gene LIKE '%$e' OR gene LIKE '%$e%' OR
pname LIKE '$e%' OR pname  LIKE '%$e'  OR pname LIKE '%$e%' OR other_names LIKE
'$e%' OR other_names LIKE '%$e' OR other_names LIKE '%$e%'");
}
?>

<table border = "10" width="300" align="center">
<tr>
<th width=>Disease</th>
<th width=>Gene Id</th>
<th> Gene</th>
<th> Gene Name</th>
<th> Gene Type</th>
<th> Chr. Number</th>
<th>Chr. Loc.</th>
<th> OMIM</th>
<th> Other names</th>

<th>Acession Id Gene</th>

<th> Protein Id</th>

<th> Protein Name</th>
</tr>

<?php
if(mysql_num_rows($sql) > 0)
{
while($row=mysql_fetch_row($sql))
{
?>
<tr>
<td width><?php echo $row[1];?></td>
```

```
<td><a href="<?php echo $row[9];?>"><?php echo $row[2];?></a></td>
<td><a href="<?php echo $row[9];?>"><?php echo $row[3];?></a></td>
<td ><?php echo $row[4];?></td>
<td><?php echo $row[5];?></td>
<td><?php echo $row[6];?></td>
<td><?php echo $row[7];?></td>
<td><a href="<?php echo $row[16];?>"><?php echo $row[8];?></a></td>
<td><?php echo $row[10];?></td>
<td><a href="<?php echo $row[12];?>"><?php echo $row[11];?></a></td>
<td><a href="<?php echo $row[13];?>"><?php echo $row[14];?></a></td>
<td><?php echo $row[15];?></td>

<?php
}
}
?>
</div>
</div>
</div>
</div>
</div>
</body>
</html>
```

CHAPTER – 4
CONCLUSION & FUTURE PROSPECTS

This web repository will be comprehensive resource for scientists and academicians working in the area of mitochondrial and neurological diseases and disorders. Database developed and integrated in the background will provide users information as per their need and will help them to extract information regarding marker associated with disease/disorder of their choice.

Basic information has been collected and incorporated to give the geographical distribution and population statistical ratio of the diseases included in this repository. Marker information associated with mitochondrial and neurological disorders contains gene and protein information along with their hyperlinks to their original resources so user can fetch more information if required. For genetic associated information of the diseases, we have provided hyperlinked OMIM IDs for all the markers to the OMIM database.

We will extend the functionality and storage of this repository by the inclusion of more data sets and markers associated with these diseases in near future. Other mitochondrial and neurological associated disease will also be incorporated as per the availability of data.

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