Journal of Advanced Zoology

ISSN: 0253-7214

*Volume **44** Issue **S-02 Year 2023** Page **3621:3632***

Neuro Hub; an Insight to Neurological Disorders

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Article History

Received: 06 August 2023
Revised: 29 September 2023
Accepted:09 November 2023

Abstract

In a protein- protein interaction network highly connected proteins are known as hubproteins. Hubproteins play a crucial part in the modular structure of the protein interaction network. They play a fundamental part in a wide range of biological processes in a number of different ways, and theyare also to responsible for a number of diseases like cancer, auto immune disorders, and neuro degenerative illnesses. Among them the most common one is neuro degenerative disease. In orderto give information about neuro degenerative diseases brought on by hub proteins, a database called Neuro Hub was established. Electronic databases maintain data in a persistent, non- volatile form that allows operations to be repeated and compared with other operations, with the results communicated to other researchers and developers. "Neuro Hub" is a database which was developed using CSS, HTML and Javascript. It contains information on neuro degenerative diseases caused by hub proteinsgallery of neuro hubs, references and new events showing the updated information. Currently there is no database connecting hub protein and neuro degenerative disorders. Hence "Neuro Hubs remains as a primary accession point for retrieving information related to hub proteins responsible for neuro degenerative diseases. Researchers are trying to solvethe mystery and stigma associated with this disease and the discipline Bioinformatics it will be a useful one. The development of high- throughput technologies has generated large amount of sequence and structural data. These huge amounts of data are available in public domain databases but mining the specific data is quite a Herculean task. These challenges can be overcome from thedatabase"Neuro hub".

Keywords: *Hub proteins, neuro degenerative diseases, Neuro Hub, Databases.*

1. INTRODUCTION

Physical interactions between proteins are fundamental to most biological processes, since proteins need to interact with other proteins to accomplish their functions. Because of this, understanding protein interactions is essential to comprehending how biology works[1]. Because many proteins' functions are unknown, it is likely that identifying the physical interactions in whichthese proteins take part will reveal something about those interactions' functions. In a protein- protein interaction network highly connected proteins are known as hub proteins. Hub proteins play a crucial part in the modular structure of the protein interaction network[2]. Hubs have fast turnover and regulation despite being slow to evolve because of evolutionary conservation. They play a fundamental part in a wide range of biological processes in a number of different ways, and they are also to responsible for a number of diseases like cancer, auto immune disorders, and neurodegenerative illnesses[3]. Among them the most common one is neuro degenerative disease. Neurodegenerative disorders are characterized by progressive loss of selectively vulnerable populations of neurons, which contrasts with select static neuronal loss because of metabolic or toxic disorders. [4] A serious threat to human health is posed by neurodegenerative diseases. Because of the recent growth in the older population, many age-dependent illnesses are becoming more and more common [5]. Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, fronto temporal dementia, and the spinocerebellar ataxias are a few examples of neurodegenerative disorders. (Gitler). Hub proteins are the primary culprits in the majority of neurodegenerative disorders. In order to give information about diseases broughton by hub proteins, a database called Neuro Hub was established.
Maintaining electronic databases is one of the applications of the interdisciplinary field, Bioinformatics. Electronic databases maintain data in a persistent, non- volatile form that allows operations to be repeated and compared with other operations, with the results communicated to other researchers and developers [6]. One of the popular packages for developing biological databases is Javascript, HTML with CSS. This database serves as an integrated resource for information access on the hub proteins, their pathway, treatments, etc. that cause neurodegenerative disorders.

2. MATERIALS AND METHODOLOGYDISEASE DESCRIPTION

Parkinson's disease
Parkinson's disease is a brain condition that results in unintentional or uncontrollable movements like trembling, stiffness, and issues with balance and coordination [7].Typically, symptoms start out mildly and get worse over time. People could experience difficulties speaking and walking as the illness worsens. Additionally, they may experience behavioral and mental changes, sleep issues, depression, memory loss, and weariness. According to certain studies, men are more likely than women to get this condition. It's unknown why, but research is being done toidentify potential risk factors. Age is an obvious risk [8]: Although roughly 5% to 10% of Parkinson's patients suffer beginning before the age of 50, the disease often first manifests in thoseover the age of 60. Parkinson's disease with an early onset is frequently inherited, but not always, and some kinds have been connected to particular genetic changes. The basal ganglia, a region of the brain that regulates movement, experiences nerve cell impairment and/or death, which resultsin the most noticeable signs and symptoms of Parkinson's disease. These nerve cells, or neurons, normally generate the crucial brain neurotransmitter dopamine. Movement issues connected withthe condition are brought on by decreased dopamine production as a result of neurons that have died or been damaged [9].

Norepinephrine, the primary chemical messenger of the sympathetic nervous system, which regulates numerous bodily functions like heart rate and blood pressure, is also lost in peoplewith Parkinson's disease [10]. Some of the Parkinson's disease non-movement symptoms, such as exhaustion, fluctuating blood pressure, slower digestion, and a sharp drop in blood pressure after rising from a sitting or laying position, may be explained by the loss of norepinephrine. Lewy bodies, peculiar clumps of the protein alpha-synuclein, are seen in numerous brain cells of Parkinson's disease patients [7]. Alpha-synuclein has both normal and pathological roles, and researchers are working to

better understand how these functions relate to genetic variations that affect Parkinson's disease and Lewy body dementia [9]. A few cases of Parkinson's disease can be linked to particular genetic mutations, and some cases of the condition appear to be hereditary. Although Parkinson's disease is known to have a genetic component, the condition rarely runs in families. Many scientists now think that a mix of genetic and environmental factors, including exposure to chemicals, causes Parkinson's disease.The major symptoms of Parkinson's disease are, Tremor in hands, arms, legs, jaw, or head[11].

Multiple Sclerosis

The most prevalent demyelinating illness, known as multiple sclerosis (MS), causes destruction tothe protective sheaths that surround nerve cells in the brain and spinal cord. This harm interferes with the nervous system's ability to transfer messages, leading to a variety of physical, mental, andoccasionally psychiatric issues as signs and symptoms [12].Double vision, visual loss, muscle weakness, and issues with sensation or coordination are only a few examples of specific symptoms.Multiple sclerosis (MS) can manifest in a variety of ways, with new symptoms either appearing suddenly (relapsing forms) or accumulating over time (progressive forms). In the relapsing types of MS, symptoms may entirely subside between attacks, but some long-term neurological issues frequently persist, especially as the disease worsens. The most prevalent immune-mediatedcondition affecting the central nervous system is multiple sclerosis. In the US, there will be closeto a million MS patients by 2022[13].

Autonomic, ocular, motor, and sensory issues are the most frequent neurological symptoms and signs in people with MS [14]. The specific symptoms depend on where the lesions are in the nervous system and may include changes in sensation such as tingling, pins and needles, or numbness; loss of sensitivity; muscle weakness; blurred vision; pronounced reflexes; muscle spasms; difficulty moving; problems with coordination; and balance problems. Other symptoms may include difficulty speaking or swallowing; visual issues; feeling tired; acute or chronic pain; and problems with bladder and bowel. Walking difficulties and a higher risk of falling can emerge as multiple sclerosis progresses. Thinking difficulties as well as emotional issues like sadness or fluctuating moods are widespread [15]. Slower information processing speed is the main cognitiveweakness that MS patients experience, with memory and executive function less frequently impaired. The degree of cognitive impairment varies greatly among MS patients, but intelligence, language, and semantic memory are typically intact. It is brought on by a confluence of environmental and genetic variables, such as infectious pathogens [16].

Lewy bodies Dementia

A kind of dementia known as dementia with Lewy bodies (DLB) is characterized by modifications in sleep, behavior, cognition, mobility, and control of automatic body activities. Notalways an early sign, memory loss. The condition increases over time and is typically identified when cognitive impairment makes it difficult to carry out daily tasks normally [17]. DLB is one of the two Lewy body dementias, the other being Parkinson's disease dementia. Although it is a prevalent type of dementia, the frequency is not precisely understood, and many cases goundiagnosed. Kenji Kosaka published the initial description of the illness in 1976. The majority ofDLB sufferers do not have any relatives who also have the condition, though this does happen rarely. Although the specific origin is unknown, aberrant protein clumps have been found to form in neurons throughout the brain [18]. These clumps influence both the central and autonomic nervous systems, manifesting as Lewy bodies and Lewy neurites, both of which were first identified by Frederic Lewy in 1912. Constipation is one of the most typical symptoms, and heartfunction as well as every level of gastrointestinal function—from chewing to defecating—can be impacted. On standing, low blood pressure can also happen. DLB frequently results in psychological symptoms as apathy, depression, or changed behavior. DLB often manifests after the age of fifty, and those who have it have an average life expectancy of roughly four years afterdiagnosis, however this is highly variable. [19] People with DLB may become

unable of caring for themselves in the later stages of the disease because there is no known treatment or therapy tostop the disease's progression. The goal of treatments is to lessen some of the symptoms and the stress on carers. Melatonin can be used for sleep-related symptoms, and drugs like donepezil and rivastigmine can briefly enhance cognition and general functioning [20].

Huntington's Disease

The neurodegenerative disorder Huntington's disease (HD), commonly known as Huntington's chorea, is largely hereditary.The first signs are frequently niggling issues with mood or mental/psychiatric capacities [21]. The result is frequently a general lack of coordination and ashaky walk. Additionally, chorea, a disorder of hyperkinetic movement, is brought on by the illness of the basal ganglia. Uncoordinated, uncontrollable body movements associated with chorea become increasingly noticeable as the illness progresses. Physical abilities eventually deteriorate to the point when coordinated movement is challenging and speech is lost. Mental faculties typically deteriorate into dementia, depressive disorders, apathy, and even impulsivity. Each individual has slightly different symptoms [22]. Although symptoms might appear at any age, they typically first appear between the ages of 30 and 50. Each subsequent generation could see the condition progress more quickly. Juvenile HD, which accounts for about 8% of cases that begin before the age of 20, often presents with chorea-like symptoms rather than the sluggish movement signs of Parkinson's disease [23].

Huntington's disease signs and symptoms can appear at any age, however they often first appear between the ages of 30 and 50. Huntington’s disease is a rare, genetic condition that results in the progressive degeneration of brain nerve cells. The functional capacities of a person are significantly impacted by Huntington's disease, which typically causes mobility, cognitive, and psychological issues. Movement, cognitive, and psychological impairments are frequently broughton by Huntington's disease, and its indications and symptoms can range greatly. It substantially differs from person to person which symptoms start to manifest initially. While some symptoms may be more prominent or have a bigger impact on functionality than others, this might alter duringthe course of the illness[24].

Alzheimer's disease

Alzheimer's disease is a brain ailment that gradually impairs thinking and memory abilities as well as the capacity to do even the most basic tasks. Symptoms of the late-onset variety typically begin to show in the majority of patients in their mid-60s.Dr. Alois Alzheimer is honoured by the disease's name. Dr. Alzheimer observed alterations in the brain tissue of a woman who had passedaway from an uncommon mental disease in 1906. Memory loss, linguistic difficulties, and unpredictable behaviour were some of her symptoms. He discovered numerous aberrant clusters (now known as amyloid plaques) and tangled bundles of fibres (now known as neurofibrillary, ortau, tangles) in her brain after she passed away.Still one of the features of Alzheimer's disease, these plaques and tangles in the brain [25]. The brain's loss of connections between nerve cells, or neurons, is another characteristic. Neurons carry signals from the brain to the body's muscles andorgans as well as between other brain regions. Alzheimer's disease is also thought to be influenced by a variety of other intricate brain alterations.The entorhinal cortex and hippocampus, as well asother memory-related brain regions, are initially damaged. Later, it impacts parts of the cerebral cortex that are involved in language, thought, and social behaviour. Eventually, the brain's many other regions suffer harm [26].

A neurodegenerative ailment known as Alzheimer's disease (AD), which greatly impairs social and vocational performance, is characterised by cognitive and behavioural impairment. It has a protracted preclinical period and a progressive course, and it is incurable. In Alzheimer's disease,plaques form in the cerebral cortex and other regions where thinking and decision-making occur, including the hippocampus, a structure located deep within the brain that aids in memory encoding.It is still unknown whether plaques are a direct cause of AD or if they are a byproduct of the AD process. One of the

most important neuroimaging findings in AD is hippocampal shrinkage, which is shown in the following picture [27].

Even though the earliest symptoms of Alzheimer's may differ from person to person, memory issues are often one of the first signs of the disease. The very early stages of Alzheimer's disease may also be indicated by a deterioration in other cognitive abilities, including the ability to express oneself clearly, problems with vision or spatial awareness, and impaired reasoning or judgement. However, not everyone who has mild cognitive impairment (MCI) will go on to acquire Alzheimer's. MCI is a condition that can be an early indicator of the disease [28].

System description

Data source

The data required for Neuro hub database were collected from literature references and through online resources. The database includes the Description, Overview, Picture gallery, Help, References, New events and pathway.

Tools Specification

The development tools used are,

HTML

HTML is the language used to create web pages. It stands for Hyper Text Markup Language. It is not a programming, but a markup language. A markup language uses a set of markup tags.HTML uses markup tags to describe web pages. HTML can include embedded scripting language code (such as JavaScript) that can affect the behavior of Web browsers and other processors. When the web client accesses the website, a default or homepage in HTML format is transmitted to the user. The HTML file can display images, sounds and multimedia objects. The objects are not actually stored in the HTML document. Instead, an external reference to a picture or multimedia object is inserted in the text of HTML document [29].

JAVASCRIPT

JavaScript is a scripting language used to enable programmatic access to objects within other applications. It is primarily used in the form of user JavaScript for the development of dynamic websites. JavaScript is characterized as a dynamic, weakly typed, prototype based language with first class functions. JavaScript is used to do user side validation. It is used to create mouse over events [30].

CSS

The process of making web pages attractive is made easier with the use of CSS, often known as cascading style sheets.The style and feel of a web page is handled by CSS. The colour of the text,the font style, the spacing between paragraphs, the size and arrangement of columns, the background pictures or colours used, layout designs, differences in display for various devices andscreen sizes, and a variety of other effects can all be controlled using CSS [31].

System Analysis

System analysis is the application of the system approach to the study and solution of problems using computer based system. System thinking is integral to system work. Organizations are complex systems that consist of the interrelated and interlocking subsystems. Changes are one partof the system having both anticipated and unanticipated consequence in other part of the system. The systems approach is a way of thinking about the analysis and design of computer trends application. It proves a framework for visualizing the organizational and environmental features that operate on a system. During the analysis phase the system is thoroughly studied keeping in mind the aim of the tool and the user requirements.

Existing system: The analysis part includes a detailed study of the existing system. Existing system

is several public domain databases which includes neuro hubs (Hub proteins responsible for neuro degenerative disease) information. Retrieval of specific information from these resources is a tedious process. There is no specificity and more over the redundancy of data.

Limitations

1. Difficulty in data retrieval.
2. Redundancy of data.
3. Lack of specificity.
4. Lack of integration of data.

All these are specified in the proposed system. Much emphasis is given up on the process of user friendly operation especially for researchers.

Proposed system

The proposed system is developed using HTML, Javascript and CSS
In this system output of the software application is a database showing informationon neuro hubs. User can select a hub proteins and related neurodegenerative diseases using simple keyword search. The software should extract the related data from database according to the user requisite. User entry should be validated before giving as query to the database. The retrieved information from the database has to be represented as webpage showing relevant information.

Analysis of the system shows the need for database application, efficient server side programming, user friendly web interface, client and administrator side validation and database connectivity. Javascript is a scripting language which satisfies all coding requirements. It has many modules for string manipulation, database connectivity (DBI), server side programming and administrator side programming. Javascript, CSS database application can be used to store information about hub proteins responsible for neurodegenerative diseases.

Web interface can be created using HTML. User entered query must be passed as HTTP request and the server side program has to validate the query. JavaScript can be used for client validation and it goes well with HTML. Database connectivity is required to retrieve data from database according to the user selection.

System Design

Design is a creative process; a good design is the key to effective system. The term "Design" is defined as "The process of applying various techniques and principles for the purpose of defining a process or a system in sufficient detail to permit its physical realization". Various design features are followed to develop the system. The design specification describes the features of the system, the components or elements of the system and their appearance to end-users.

In system design high-end decisions are taken regarding the basic system architecture, platforms and tool to be used. The system design transforms a logical representation of what a given system is required to be in to the physical specification. Design starts with the system's requirement specification and converts it into a physical reality during the development. Important design factors such as reliability, response time, throughput of the system, maintainability, etc should be taken into account.

Module Level Architecture-1

User interface program (Client side)

This deals with user interface. In simple keyword search user can use any type of keywords .If the desired keyword is used, then an intermediate page is displayed which contains the hit information on the specific neuro degenerative disease caused by hub proteins. Further searching on hit information will show detailed features of hub proteins, the disease caused by them, causes, and the pathway of related diseases.

The database also facilitates the following options;

1. Overview : It gives overall information about Neuro hub database.
2. Description : It describes the various disease caused by hub proteins.
3. Gallery : It lists the pictorial representation of neuro degenerative diseases causedby hub proteins.
4. Pathways : It contain pathways of each and every diseases
5. Hub gene table : It provides a list of hub genes and the neuro degenerative diseases causeby each hub genes
6. New Events : It shows the recent information on neuro hubs and provide web linkto access that information.
7. Enquiry & contact us: It facilitates user to query any general information on Neuro Hub

System Implementation

Methodology

Implementation is the stage of the project where the theoretical design is turned into a working system. If the implementation is not carefully planned and controlled it can cause chaos and confusion. The new system may totally replace existing system or it may be major modification toan existing system. The process of putting the developed system in actual use is called system implementation. This includes all those activities that take place to convert from the old system toa new system. The system can be implemented only after thorough testing is done and it is foundto be working according to the specification of the system.

Waterfall Model

The waterfall model is a sequential software development process, in which progress is seen as flowing steadily downwards through the phase of Analysis, Design, Implementation, Testing and Maintenance. All these phases are cascaded to each other so that second phase is started as and when defined set of goals are achieved for first phase and it is signed off. All possible requirements of the system to be developed are captured in the analysis phase. Requirements are set of functionalities and constraints that the end-user expects from the system. The requirements are analyzed for their validity and the possibility of incorporating the requirements in the system to be developed is also studied. Finally, a requirement specification document is created which serves the purpose of guideline for the next phase of the model. The requirement specifications are studied and system design is prepared. System design helps in specifying hardware and software requirements and also helps in defining overall system architecture. The system design specifications serve as input for the next phase of the model. On receiving system design documents, the work is divided into modules/ units and actual coding is started. The system is first developed in small programs called units, which are integrated in the next phase. Each unit is developed and tested for its functionality; this is referred to as Unit Testing. Unit testing mainly verifies if the modules/ units meet their specifications, These units are integrated into a complete system during Integration phase and tested to check if all modules/ units coordinate between each other and the system as a whole behaves as per the specifications. After successfully testing the software, it is delivered to the user.

Requirement Analysis

The requirements were:

- Database containing information about neuro hubs
- Database connectivity.
- Web interface to take input from user.
- module to display neuro hub data.

Design

System Design helps in specifying and system requirements and also helps in defining overall system architecture. The hardware requirements include Hard Disk, RAM, and Processor etc. The software requirements include HTML, JavaScript, CSS etc.

Coding
The system design specification is translated into computer code using a programming language. Javascript, HTML and CSS are the programming languages used for coding.

Testing
Testing is done to check whether the application is running without any problem; testing is done both manually and through program. Manually different keyword can be given as input to check whether any error exists.

Maintenance
The maintenance phase is usually the longest stage of the software. In this phase the software is updated to:
Meet the changing customer needs. Adapted to accommodate changes in the external environment. Correct errors and oversights previously undetected in the testing phase. Enhancing the efficiency of the software.

System Testing
Testing is the process of executing a program with the intent of finding error. The purpose of the system testing is to identify and correct bugs in the developed system. Nothing is complete without testing. If a system has been found free of errors after sufficient amount of testing it can be implemented. System testing makes a logical assumption that if all part of the system is correct the goal will be successfully achieved.

- Test case defines the input and output behavior of the system.
- Test procedure defines how a program may be validated against test data.

System testing is the process of analyzing a system to detect the differences between existing and required conditions and to evaluate the features of the system. System testing is an activity that should be done throughout the whole development process.

Unit Testing
Unit testing is the testing of individual hardware or software units or groups of related units. The administrator carries out unit testing in order to check if the particular module or unit of code is working fine. The unit testing comes at the very basic level as it is carried out as and when the unit of the code is developed or a particular functionality is built.

Integration Testing
Integration test is testing in which software components, hardware components or both are combined and tested to evaluate the integration between them. This test verifies that units work together when they are integrated into a larger code base. Just because the components work individually, that doesn't mean that they all work together when assemble or integrated.

Functional Testing
In this type of testing, the software is tested for the functional requirements. The tests are written in order to check if the application behaves as expected. Functional testing covers how well the system executes the functions it is supposed to execute-including user commands, data manipulation, searches and integrations.

3. RESULT AND DISCUSSION

A database is an information store, we can store all type of data within that and can also access the information from that at anytime, anywhere.A biological database is a collection of biological data organised in a machine-readable format for faster search and retrieval and ease of use.Databases are crucial tools that let scientists analyse and explain a wide range of biological phenomena, including

the interactions and structures of biomolecules, an organism's whole metabolism, and the evolutionof species.Hub proteins are those proteins in a system of protein-protein interaction networks that have noticeably more interaction relations (or degrees) than the other proteins. The biological relevance will rise along with the number of interacting proteins. Human disorders caused by hub proteins are numerous, among them neurodegenerative diseases being the most prevalent one.

Neuro Hub is a repository of human neuro hub proteins. It provides access to various hub proteins responsible for neuro generative diseases. It contains information about the list of hub proteins responsible for neuro degenerative diseases, causes, symptoms, pathways, medications additional features such as description on neuro degenerative diseases, a gallery of neuro hubs, references and new events showing the updated information. It also contains information about the pathway of neuro degenerative diseases. The database can be searched by using simple keyword. Currently there is no database providing information regarding hub proteins related neuro degenerative diseases, hence this database will provide more insight to those who are much interested in hub protein and neurodegenerative disease studies.

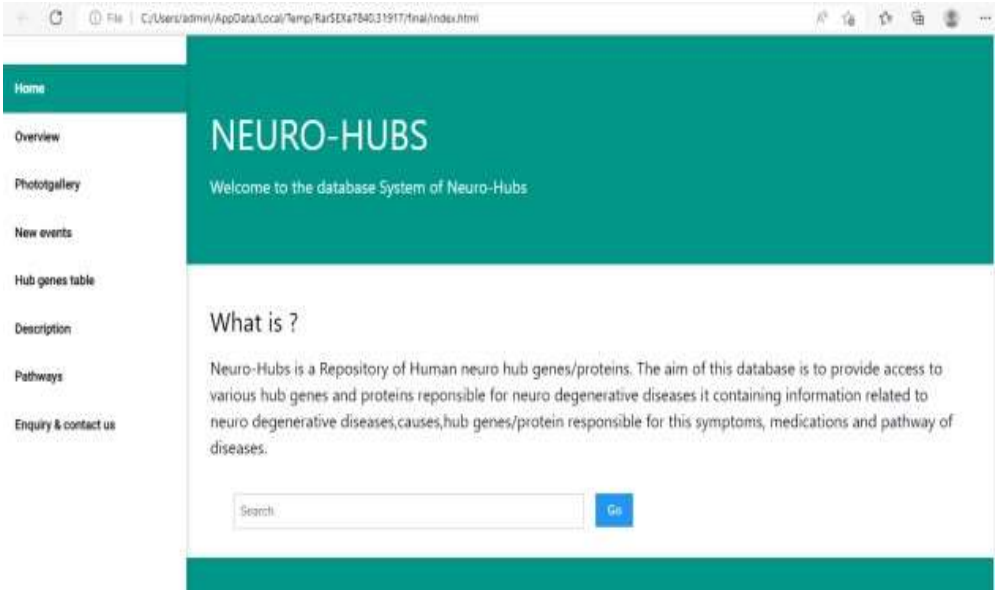

Figure 1: Neuro Hub home page

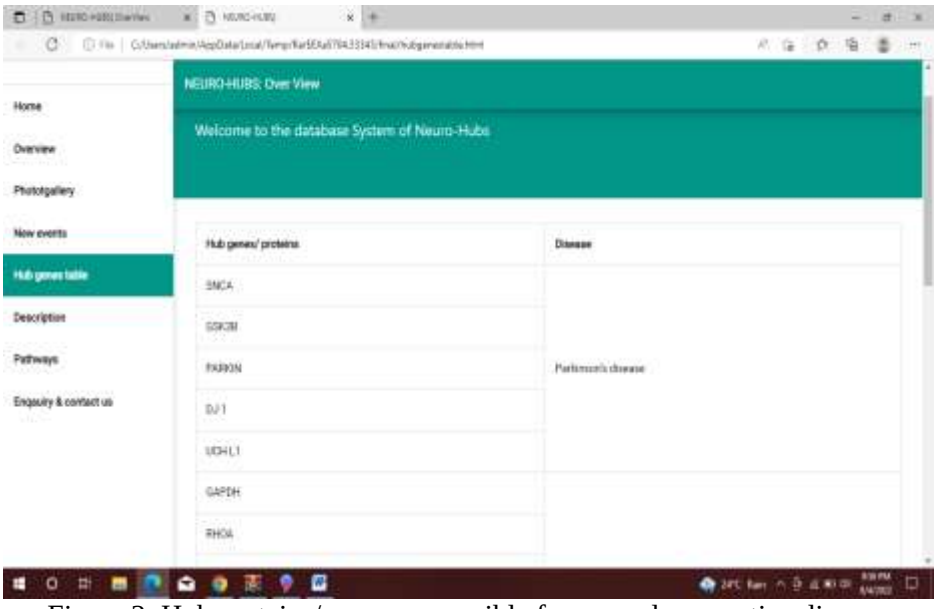

Figure 2: Hub proteins/genes responsible for neurodegenerative disease

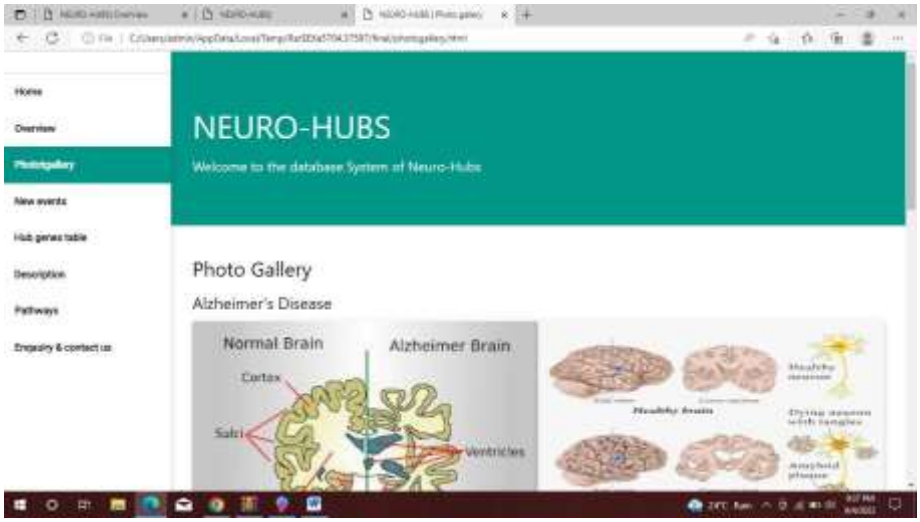

Figure 3: Photo gallery of Neuro hub

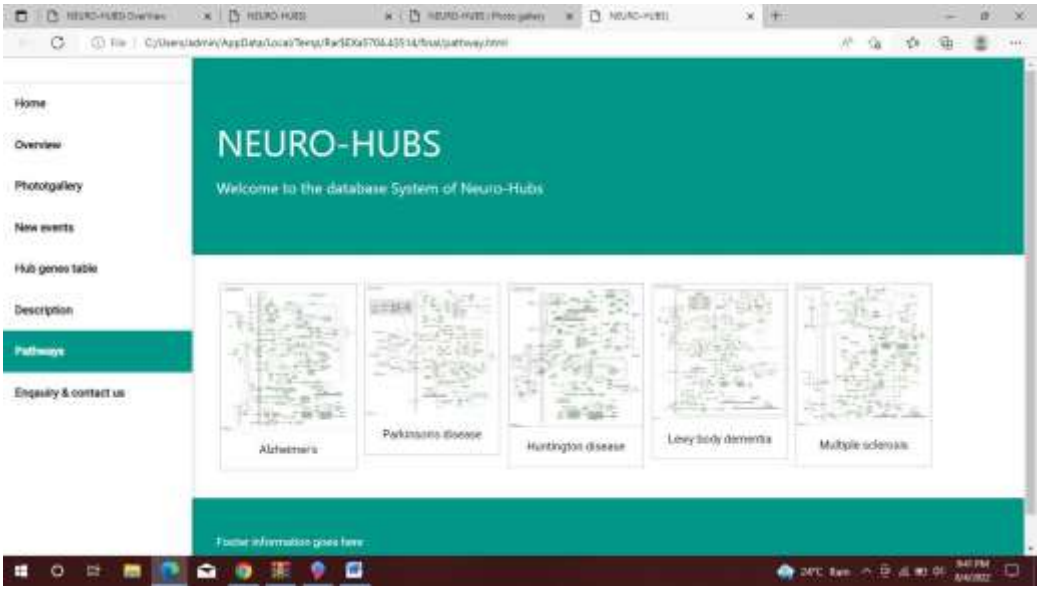

Figure 4: Pathways of neurodegenerative diseases

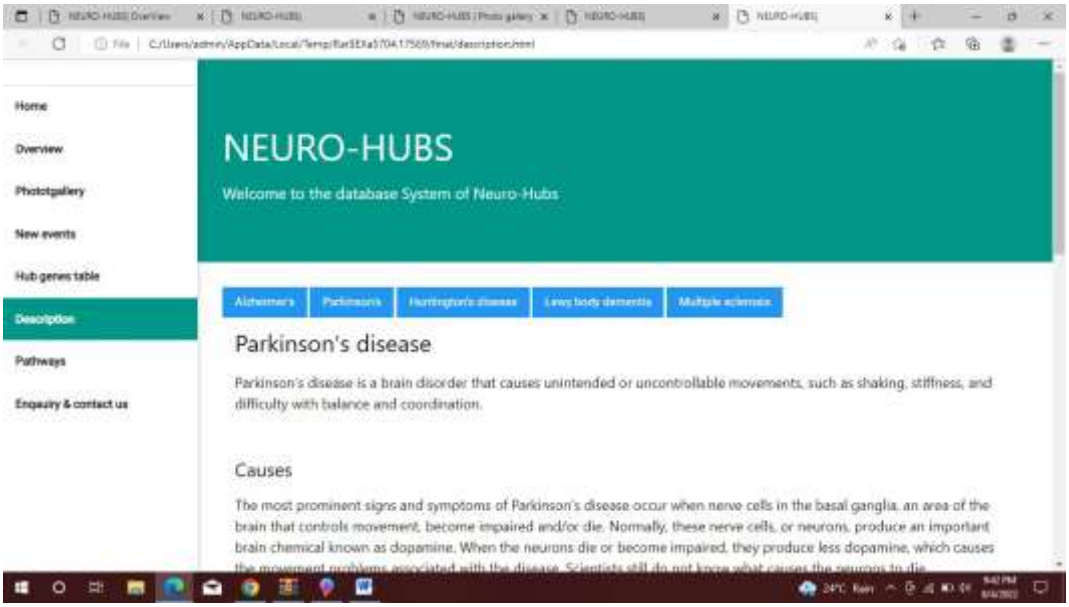

Figure 5 : Description page of Neuro hub

4. CONCLUSION

The challenges posed by hub proteins induced neuro degenerative disease have seeked a global attention. Researchers are trying to solve the mystery and stigma associated with this disease andthe discipline Bioinformatics can help them in a greater extend. The development of high- throughput technologies has generated large amount of sequence and structural data. These huge amounts of data are available in public domain databases but mining the specific data is quite a Herculean task. These challenges can be overcome from the database "Neuro hub".

"Neuro Hub" is a database which was developed using CSS, HTML and Javascript .It contains information on neuro degenerative diseases caused by hub proteins. The information includes the list of hub proteins responsible for neuro degenerative diseases, causes, symptoms, pathways, medications additional features such as description on neuro degenerative diseases, a gallery of neuro hubs, references and new events showing the updated information. The database can be searched by using simple keyword.It also provides cross-reference to other public domain databases. Thus "Neuro Hubs "helps researchers by providing a specific and integrated data. Moreover it remains as a primary accession point for retrieving information related to hub proteins responsible for neuro degenerative diseases.

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