A Simulation based Approach for Detection of Retinitis Pigmentosa using Protein Synthesis

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ABSTRACT

Proteins are the basis of all organisms. Abnormality on any part of the human body can easily be detected by referring to the protein structure on that particular part. To determine any deformation in the protein structure different experimental techniques are used. Human eye is the most sensitive organ of human body. As in all parts of the body, it also contains proteins. Peripherin 2 is the most distinct protein in human eye. It is found in the rod and cone cells of the retina of the eye. This protein is encoded by PRPH2 gene. Any deformation in this protein results in one important eye disease known as retinitis pigmentosa (RP7). The person with this disease suffers from incurable blindness. In this paper, a technique is developed to detect any deformation in the structure of Peripherin2 protein by implementing three classifiers. The first classifier detects the chemical components of the amino acids then detects the amino acids and finally the system recognizes the Peripherin2 protein and the changes that occur in the chemical structure of peripherin2 during retinitis pigmentosa.

Keywords: Peripherin-2, Retinitis Pigmentosa, Aminoacids, Retina

1. INTRODUCTION

Blindness or serious vision impairment is one of the most feared disabilities known to humankind. Retinitis pigmentosa is a clinically and genetically heterogeneous group of hereditary disorders in which there is progressive loss of photoreceptor and pigment epithelial function. The prevalence of retinitis pigmentosa is between 1 in 3000 and 1 in 5000 making it one of the most common causes of visual impairment in all age groups. It causes severe vision impairment and often blindness. Retinitis Pigmentosa is a problem related to the biomedical field which deals with the detection and analysis of opacity in the glycoprotein Peripherin-2 present in the outer segment of the rod and cone photoreceptor cells of the eye. Peripherin 2 may function as an adhesion molecule involved in stabilization and compaction of outer segment disks or in the maintenance of the curvature of the rim. This protein is essential for disk morphogenesis. People suffering from retinitis pigmentosa will experience symptoms like difficulty in night vision(night blindness), no central vision, blurry vision, poor color separation and extreme tiredness[1]. In addition, RP can be accompanied by cataract [11],open-angle glaucoma, refractive errors, keratoconus,optic nerve head drusen and cystoid macular oedema [12]

Retinitis Pigmentosa can run in families. The disorder can be caused by a number of genetic defects. The cells controlling night vision (rods) are most likely to be affected. However, in some cases, retinal cone cells are damaged the most. The main sign of the disease is the presence of dark deposits in the retina. Symptoms often first appear in childhood, but severe vision problems do not usually develop until early adulthood.

2. BACKGROUND

2.1 History

Retinitis pigmentosa (RP) encompasses a large group of hereditary diseases of the posterior segment of the eye characterised by degeneration, atrophy and finally loss of photoreceptors and retinal pigment epithelium (RPE), leading to progressive visual loss. The term 'retinitis' refers to an inflammatory component.The term 'pigmentosa' refers to the pigmentary changes with a perivascular 'bonespicule' configuration in the fundus of the eye as shown in figure 1. From the detailed survey from different literatures it is observed that a method named Electroretinography is used primarily for the diagonosis of retinitis pigmentosa.[1] This detects the documentation of progressive loss in photoreceptor cells. From color vision, pupil reflex response, intraocular pressure it can also be detected. Retinal opthalmoscopy and slit lamp examination are another methods to detect retinitis pigmentosa. On the basis of any one of the test mentioned above and by referring the family history finally it can be declared that a person is suffering from retinis pigmentosa. This disease is primarily due to the X linked manner autosomal gene which is dominant in male. Therefore males are affected mostly by this disease. Till date there is no significant technique for curing this disease permanently. But it may be controlled or slow down by the antioxidants such as high dosage of vitamin A. again it has side effects such as taking high dosage of vitamin A causes serious liver problem[10]. So techmique for treatment of this blindness is still a ongoing research. The mode of inheritance of retinitis pigmentosa is determined by family history. Management of RP is very difficult because there are no proven methods of treatment. Studies have shown 15,000 IU of vitamin A palmitate per day may slow the progression, though this result is controversial. Low vision rehabilitation, long wavelength pass filters, and pedigree counseling remain the mainstay of management. Currently there is no cure for retinitis pigmentosa, but treatments are now available in some countries. However, taking high doses of vitamin A can cause serious liver problems. RP has a unique set of clinical characteristics that make it a complex disease associated with distinct inheritance patterns.

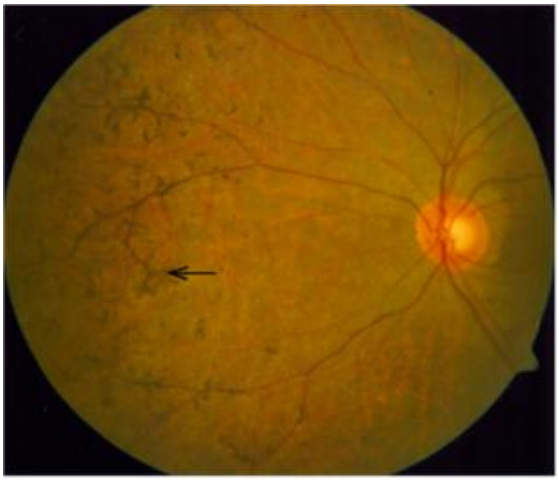

Figure 1: Fundus photograph of a patient with retinitis pigmentosa

An understanding of the pathogenesis is essential in the process of the differential diagnosis and the development of treatment options. Recent developments in research are likely to expand the various therapeutic modalities to include gene therapy, pharmacologic treatment, cell transplantation, and neuro-prosthetic devices.

2.2 Basic Biological Concept

The eye is one of nature's complex wonders. The human eye is an organ which reacts to light for several purposes. As a conscious sense organ, the mammalian eye allows vision. Eyes are organs that detect light and convert it into electro-chemical impulses in neurons.[1]

There are several other fatal eye diseases based on protein synthesis like- Cataract, Stargardt disease, Choroideremia, Oguchi disease, Vitelliform Mascular Dystrophy, etc. Out of all these diseases, Retinitis Pigmentosa is the most common inherited genetic vision impairment. It is an incurable blindness caused by abnormalities of the photoreceptors (rods and cones) or the retinal pigment epithelium (RPE) of the retina leading to progressive sight loss. The following points describes the basis behind the formation of retinitis pigmentosa-

2.2.1 Formation of Retinitis Pigmentosa (RP7) in human eye

The basis behind the formation of retinitis pigmentosa is the opacities present in the rod and cone cells of the eye or in the retinal pigment epithelium. Affected individuals may experience defective light to dark, dark to light adaptation or nyctalopia (night blindness), as the result of the degeneration of the peripheral visual field (known as tunnel vision). Sometimes, central vision is lost first causing the person to look sidelong at objects.

2.2.2 Peripherin 2 factor

Peripherin-2 is a protein, that in humans is encoded by the *PRPH2* gene. Peripherin-2 is found in the rod and cone cells of the retina of the eye. . In humans, the PRPH2 gene encodes for 173 amino acid residues polypeptide. The aminoacid sequence is as follows:

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MALLKVKFDQ    KKRVKLAQGL    WLMNWFSVLA
GIIIFSLGLF    LKIELRKRSD    VMNNSESHFV
PNSLIGMGVL    SCVFNSLAGK    ICYDALDPAK
YARWKPWLKP    YLAICVLFNI    ILFLVALCCF
LLRGSLENTL    GQGLKNGMKY    YRDTDTPGRC
FMKKTIDMLQ    IEFKCCGNNG    FRDWFEIQWI
SNRYLDFSSK    EVKDRIKSNV    DGRYLVDGVP
FSCCNPSSPR    PCIQYQITNN    SAHYSYDHQT
EELNLWVRGC    RAALLSYYSS    LMNSMGVVTL
LIWLFEVTIT    IGLRYLQTSL    DGVSNPEESE
SESEGWLLEK    SVPETWKAFL    ESVKKLGKGN
QVEAEGAGAG QAPEAG
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Where each letter represents amino acids. Eg-M represents the aminoacid Methionine, D is Aspartic acid, V is valine, T is Threonine, I is Isoleucine and so on.

2.3 Technological Concept

A simulation based system has been developed to detect the changes that occur in the protein Peripherin-2 during Retinitis Pigmentosa(RP7). For this approach MATLAB version 7.8 is used as the soft computational tool. MATLAB, which stands for MATrix LABoratory, is a software package developed by MathWorks, Inc. to facillitate numerical computations as well as some symbolic manipulation. MATLAB is a numerical computing environment and fourth generation programming language. MATLAB allows matrix manipulation, plotting of functions and data, implementation of algorithms, creation of user interfaces, and interfacing with programs in other languages.

3. NECESSITIES OF DETECTING PERIPHERIN

Presently, Perpherin-2 detection attained great interest in the field of biomedical research due to the following reasons:

- Peripherin-2, being an important soluble protein present in the eye-lens can be used to detect retinitis pigmentosa by measuring the crystalline dimensions.

- A measure of the peripherin-2 remaining in the eye lens may reflect the level of protective reserve in the photoreceptor cells and finally detects the presence of opacities in the lens.

4. METHODOLOGY

In this paper, a classifier has been designed which can detect the abnormality in the chemical structure of peripherin-2 protein which happens during Retinitis Pigmentosa(RP7). This work is summarized in the system block diagram given in Fig 1. It consists of the following steps:

4.1 Selection of Data

In our work we have considered the protein peripherin-2 which consists of 346 aminoacid residues. Amino acids are the essential medium through which the human gene translates into proteins. Primarily there are 20 amino acids but in addition to these 20 aminoacids, there are some other amino acids found in the human body but they are not constituents of proteins[7].

The chemical components that form the basis of these aminoacids are carbon, hydrogen, oxygen, nitrogen and sulphur. Each amino acid has a carboxyl group (COOH) and an amine group (NH_2), a hydrogen atom and a specific side chain (R-group) bonded to the same carbon atom which is named as α carbon atom shown in figure 2.

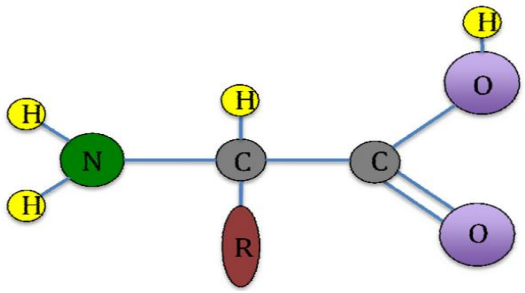

Figure 2. Structure of aminoacid.

A brief description of all the 20 different aminoacids are given below:

- Glycine: It is the smallest of all α aminoacids. Glycine helps trigger the release of oxygen required for making new cells. It is important for the manufacturing of hormones responsible for a strong immune system [4].
- Alanine: Alanine is simply glycine with a methyl (CH_3) group. Alanine is an important source of energy for muscle tissue, the brain and central nervous system. [3].
- Proline: Formally proline is not an aminoacid, it is an iminoacid. Nonetheless it is called an aminoacid. Proline is extremely important for the proper functioning of joints and tendons, and also helps maintain and strengthen the heart muscle [4].
- Valine: It is found in the interior of globular proteins. Valine promotes mental vigor, muscle coordination, and calm emotions [5].
- Leucine: It is an aminoacid with a branched hydrocarbon side chain. It provides ingredients for the manufacturing of other essential biochemical components in the body, some of which is utilized for the production of energy, stimulants to the upper brain, and promotes alertness [3]
- Isoleucine: It is one of the three amino acids having branched hydrocarbon side chains which is used in stimulating the brain in order to produce mental alertness [4]
- Methionine: It is a sulphur containing aminoacid. Methionine as the free aminoacid plays several important roles in metabolism. It functions at initiating the translation of messenger RNA [5].
- Phenylalanine: It is quite hydrophobic and a derivative of alanine which profoundly affects rain cells at the biochemical level [4].
- Tyrosine: It is an aromatic aminoacid transmits nerve impulses to the brain. It helps overcome depression, improves memory, increases mental alertness and promotes the healthy functioning of thyroid, adrenal and pituitary glands [4].
- Tryptophan: It is the largest of all aminoacids and a derivative of alanine. This is particularly needed in the body for the production of vitamin B3 [2].
- Serine: It is one of two hydroxyl aminoacids which helps strengthen the immune system by providing antibodies and synthesizes fatty acid sheath around nerve fibers.
- Threonine: It is another hydroxyl containing hydrophilic aminoacid. It helps in maintaining protein balance and in assisting collagen formation [3].
- Cysteine: It is a sulphur containing amino acid which plays a crucial role in metabolic process of many important enzymes [2]
- Asparagine: It is the first amino acid discovered in 1806 and the amide of aspartic acid which is needed mainly to maintain the homeostatic balance in the nervous system. [5]
- Glutamine: It is the amide of glutamic acid and is uncharged under all conditions. It enhances immune system. Apart from that, glutamine possesses anti-anxiety property that permits the mind to be relaxed [4].
- Lysine: It is basically alanine with a propylamine substituent on the β carbon. A deficiency of Lysine may result in fatigue, inability to concentrate, irritability, bloodshot eyes, retarded growth, hair loss, anemia, & reproductive problems [5].
- Histidine: It is an essential aminoacid with a positively charged imidiazole functional group. Histidine is found abundantly in hemoglobin [2].
- Arginine: Synthesized normally in the body, arginine is known to be a semi essential amino acid. It plays an important role in nitrogen metabolism [4]
- Aspartic acid or Aspartate: It is one of the two acidic aminoacids. It promotes enzyme activity, maintenance of solubility in the body, as well as homeostasis in ionic characters of proteins [5]
- Glutamic acid or Glutamate: It has one additional methylene group in its side chain than that of aspartic acid. It is considered to be nature's "brain food" because it improves mental capacities; helps speed the healing of ulcers, relieves fatigue, and helps control alcoholism, schizophrenia and the craving for sugar. [3]

The chemical components of all these 20 aminoacids structures are taken as input to the first system.

4.2 Generation of the Coding Scheme of Peripherin-2

Based on the chemical structure of aminoacids, a coding scheme is generated to detect the protein peripherin-2. Unique BCD codes are used for coding each component or symbol in the chemical structure of these aminoacids. Considering the chemical components, each of the components is coded using the generated coding scheme. These codes are then given to system I as input. Then the 20 amino acids are coded with the help of the coded chemical structure based on the hydrophilic and hydrophobic indexes of the aminoacids using system II. The considered protein peripherin-2 is coded with the help of coded amino acids using system III. The system model shown in Figure 3 comprises of three systems for detection of peripherin-2. The first system (System I) uses the chemical components as inputs and provides their necessary coding. The second system (System II) provides the identification of the aminoacids. The third system (System III) uses the coded aminoacids as inputs and finally detects peripherin-2 protein.

4.3 System Design and Implementation:

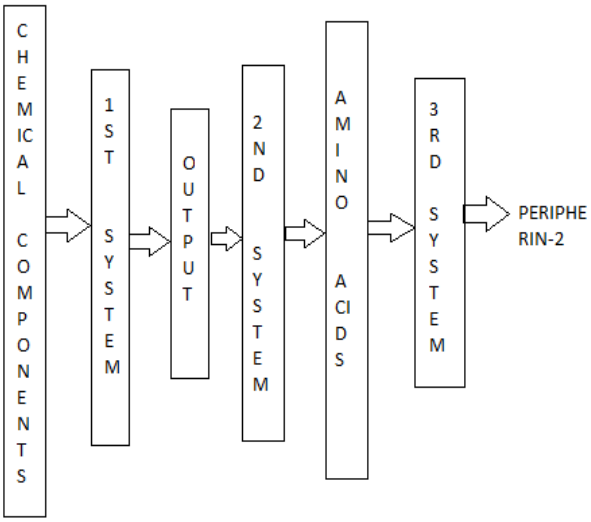

Figure 3: System Model of the proposed work.

The entire work may be summarized by the following steps—

- The first step involves the extraction and coding the chemical components present in the aminoacids.
- The second step comprises of extracting the chemical structure of the aminoacids.
- Aminoacids coding based on the hydrophobic and hydrophilic indexes is the third step.
- The fourth step is to extract the aminoacid sequence of peripherin-2 protein.
- The final step involves the detection of the protein peripherin-2.

5. RESULTS

With the 346 aminoacid residues of Peripherin-2, the proposed system using MATLAB version 7.8 shows 98% accuracy. This work shows a simulation based approach to detect the eye-lens protein peripherin-2. The first system is configured to handle different coded values of the chemical components. The second system identifies the amino acids and the third system recognizes Perpherin-2. These three systems are based entirely on the coding of peripherin-2 and the coding scheme is again based on each and every amino acid and the chemical components present in their chemical structure. As it covers all the components of the aminoacid sequence therefore the accuracy level is very high in this case.

Figure 4 represents the percentage of Peripherin-2 as pie diagram where the 20 different aminoacids are represented by different colors.

When a person suffers from Retinitis Pigmentosa 7(RP7) due to the mutation in peripherin-2 gene, certain structural changes occurs in the aminoacid sequence of peripherin-2.

- Arginine13 and Arginine142 both are substituted by Tryptophan.
- Leucine45, Leucine126 and Leucine185 are substituted by Phenylalanine, Arginine and Proline respectively.
- Lysine153 is replaced by Arginine.
- Cysteine165 and Cysteine214 are replaced by Tyrosine and Serine respectively.
- Aspartic acid173 is replaced by Valine.
- Glycine208 and Glycine266 are both replaced by Aspartic acid.
- Proline210 and Proline216 are replaced by Serine and Leucine respectively.
- Phenylalanine211 is substituted by Leucine.
- Serine212 is substituted by Glycine.
- Asparagine244 is substituted by Lysine

Figure 5 represents the percentage of substituted structures of Peripherin-2 during retinitis pigmentosa 3 as pie diagram where the 20 different aminoacids are represented by different colors.

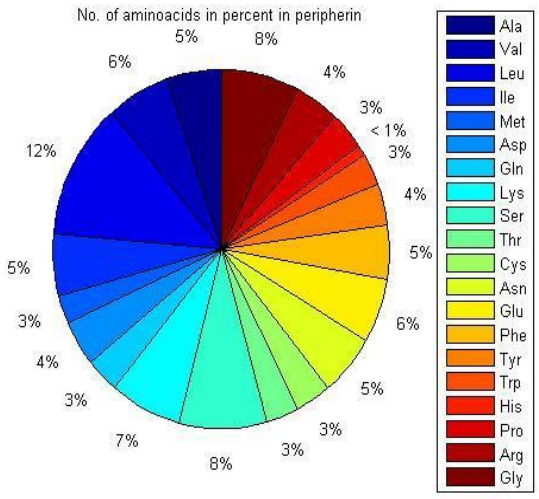

Figure 4: Structure of Peripherin-2 in percent.

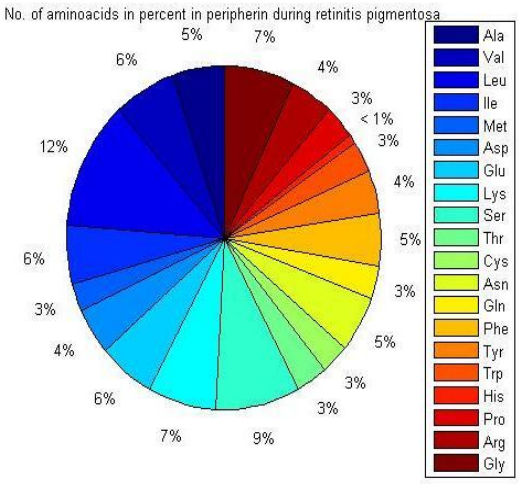

Figure 5: Structure of Peripherin-2 in percent during Retinitis Pigmentosa

It is observed that changes occur in the percentage of different aminoacids structures during RP7. In peripherin-2, glycine occupied 8% in the pie chart whereas during RP7 due to mutation in the PRPH2 gene glycine occupies 7%. Similar changes can also be seen in glutamic acid, serine, isoleucine and aspartic acid respectively.

6. CONCLUSION

Retinitis pigmentosa is a very serious genetic disease and currently there is no cure for this disease. So by synthesizing peripherin-2 protein which is responsible for this disease, preventive measures can be taken in the embryonic stage. The ease with which the simulation using MATLAB approach provides the detection of the protein-peripherin-2 makes it possible for similar applications. The success rate achieved in the detection makes the proposed approach reliable means of study of peripherin-2.

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