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In-Silico Analysis of Retinoblastoma-Associated Genes

by

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I would like to dedicate this thesis to Allah Almighty, my parents and teachers

CERTIFICATE OF APPROVAL

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(Sadaf Saeed)

Abstract

The most frequent malignant juvenile eye tumor that starts in the developing retina is called retinoblastoma (RB). The *RB1* tumor suppressor gene undergoes biallelic inactivation to start it off. There are two types of RB: hereditary and non-hereditary. Non-heritable RB usually manifests as unilateral tumors, whereas cases of hereditary RB usually show signs of bilateral tumors. Somatic mutations result in non-heritable illness, but germline *RB1* mutations cause hereditary RB. Therefore, identifying recurrence risk and directing clinical management of patients and families depend on the ability to distinguish between germline and somatic *RB1* mutations. The *RB1* gene spans 183 kb of genomic material and is found on chromosome 13q14.2. It is composed of 27 exons. The mutation spectrum of *RB1* exhibits heterogeneity, encompassing tiny insertions/deletions (indels), structural variants (SVs), and single nucleotide variations (SNVs).

The objective of this study is to predict and analyze the genes associated with retinoblastoma, a cancerous tumor that forms in the retina. To achieve this, we utilized text mining techniques to identify genes that could potentially be linked to retinoblastoma. After the first prediction of genes, additional study was carried out to ascertain the precise roles and biological processes associated with them. We undertook further study to investigate the involvement of these genes in retinoblastoma-related pathways with the aim of obtaining a deeper understanding of their function in the disease progression. Ultimately, we confirmed the connections of cluster proteins by utilizing the ProteinPrompt server, thereby proving the functional importance of these proteins in relation to retinoblastoma. This comprehensive approach provides new understandings of the molecular mechanisms behind retinoblastoma and proposes potential targets for therapeutic intervention.

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Abbreviations

BP	Biological process
CC	Cellular component
ceRNA	Competing endogenous RNA
DAVID	Database for Annotation, Visualization and Integrated discovery
DEGs	Differentially expressed genes
DERBGs	Differentially expressed retinoblastoma genes
GEO	Gene expression omnibus
KEGG	Kyoto encyclopedia of genes and genomes
MF	Molecular function
PPI	Protein–protein interaction
RB	Retinoblastoma
STRING	Search tool to retrieve interacting genes and proteins

Chapter 1

Introduction

Benedict was the first person to report retinoblastoma (Rb), a rare form of childhood cancer, in the published medical literature [1]. This condition originates in the retina, which is the light-sensitive tissue that lines the back of the eyeball and contains cells that have not yet matured. From the time of birth until approximately the age of five years old, Rb is found in very young children. The Rb subtype accounts for approximately three percent of all cases of cancer in children younger than fifteen years old [2].

Rb is distinguished by the rapid growth of tumors within the retinal tissue, which is one of its characteristics. It is estimated that survival rates for Rb are among the highest for pediatric cancers in developed nations, ranging from 95 to 98 percent percent. Because of this, it can be concluded that more than nine out of ten patients with Rb will survive into adulthood [2, 3].

There are two presenting kinds of retinoblastoma: heritable and non-heritable. It is common for the hereditary form to involve tumors in both eyes, although there are instances in which only one eye is affected. When it comes to the non-heritable form, the tumor is only found in one eye [1]. The non-heritable form of retinoblastoma accounts for approximately 55% of all documented cases [2]. In cases where there is no history of the disease in the patient's family, retinoblastoma is referred to as "sporadic." It is important to note that the occurrence of sporadic cases does not necessarily indicate the non-genetic form [3].

In approximately two-thirds of cases, the development of unilateral retinoblastoma takes place, while bilateral retinoblastoma takes place in the remaining third of cases. A number of factors, including the number of tumors, their size, and their location, as well as the possibility of involvement of the pineal gland (trilateral Rb), play a role in determining the treatment option for Rb (Fig 1.1) [2, 4].

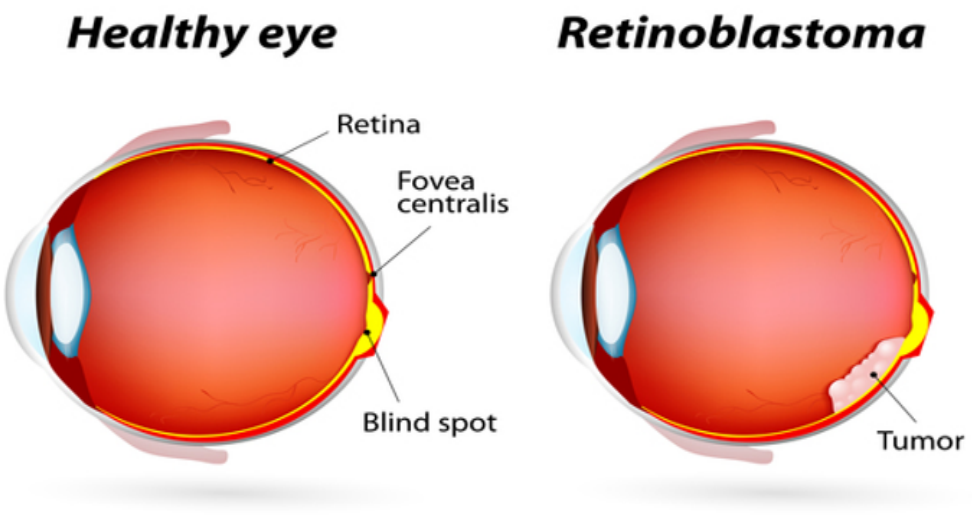


FIGURE 1.1: Description of healthy and retinoblastoma eye.

Retinoblastoma is characterized by an abnormal white reflection in the pupil, which is known as leukocoria [4]. This is the most common and noticeable sign of the disease. Some additional possible symptoms include a decline in vision, redness and irritation of the eye, and a delay in the development of the child [2]. Strabismus, also known as squinting or crossed eyes, is a condition that can develop in some children who have retinoblastoma. This misalignment of the eyes is the cause of terms such as "cross-eyed" and "wall-eyed" being used to describe the individuals' appearance [3, 5, 6].

It is common for Rb to present with advanced disease in developing countries, which can be identified by the presence of eye enlargement. When performing a routine eye exam with an ophthalmoscope, the visibility of the tumor is dependent on the patient's position. In most cases, a confirmed diagnosis requires the patient to be under anesthesia. The presence of a white pupil, which may be indicative of retinoblastoma, does not necessarily indicate the presence of the disease (Fig

1.2). Leukocoria, also known as white eye reflection, can be caused by a number of factors, including poor light reflection and other conditions such as Coats' disease. In photographs, the presence of retinoblastoma can be indicated by the presence of asymmetry, which occurs when one eye exhibits red-eye as a result of the flash while the other eye does not [3].

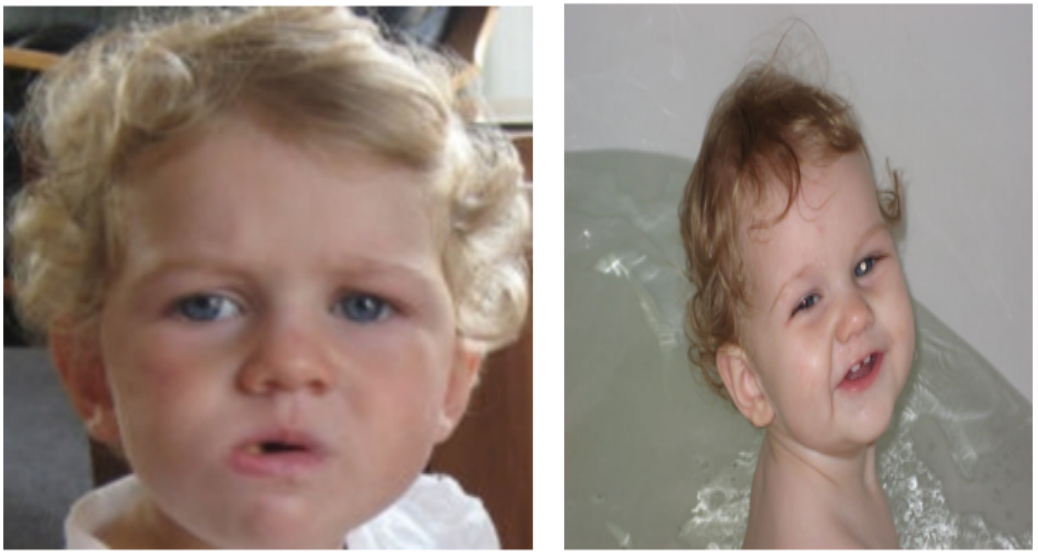


FIGURE 1.2: Display of crossed eyes (strabismus), and cat's eye reflex.

Retinoblastoma is a rare form of pediatric eye cancer that typically presents itself prior to the age of five, typically in the very early stages of childhood [4]. Where it all begins is in the retina, which is the light-sensitive lining that is located at the back of the eye. In spite of the fact that the majority of cases of retinoblastoma only affect one eye, approximately one in three children who are diagnosed with this cancer also develop tumors in both of their eyes [5]. The "cat's eye reflex" or leukocoria, which is characterized by a white shine in the pupil, is the most characteristic indicator that can be observed. When the light is low or when the flash is being used for photography, the most obvious signs of this aberrant reflection are present [6].

Additional symptoms include altered iris color, redness, pain, or swelling of the eyelids, as well as blurred or impaired vision in the affected eye or eyes. Strabismus, also known as crossed eyes, is another symptom. Retinoblastoma can spread beyond the eye and become a life-threatening condition if it is not treated in a timely manner; however, if it is diagnosed early, treatment can be successful [5, 6].

It is essential to make a prompt diagnosis and begin treatment as soon as possible in order to effectively manage retinoblastoma [1]. Retinoblastoma has a high rate of cure when it is detected at an early stage [2]. Regrettably, the malignancy claims the lives of the great majority of youngsters afflicted with it worldwide, especially in underdeveloped nations. Roughly 87 percent of patients around the world pass away from retinoblastoma, which is frequently the result of delayed detection [4]. Despite the fact that survival rates are significantly higher in developed countries, 97% of those who survive have some form of moderate to severe vision impairment. One or both of the eyes may become blind for some people [4]. Despite the fact that treatment priorities for retinoblastoma vary from country to country, the primary objectives are to save the child's life, preserve vision to the greatest extent possible, and reduce the number of complications that occur during treatment [5]. Recent efforts have been made to investigate potential alternatives to enucleation and radiation therapy, with a particular focus on local treatments as well as conventional and high-dose chemotherapy for the purpose of achieving curable outcomes [7, 8].

1.1 Treatment of Retinoblastoma

There are a number of reputable medical centers in Pakistan that provide cutting-edge diagnostics and treatment options for retinoblastoma in individuals who are children. Imaging that utilizes multiple modalities and a variety of therapeutic options are both available.

1.1.1 Main Retinoblastoma Treatment Approaches

The main retinoblastoma treatment approaches include chemotherapy which is used to reduce the size of tumors through anti-cancer drugs. It is common practice to administer a course of treatment for retinoblastoma that lasts for six months in order to achieve the greatest possible reduction in the size of the tumor prior to administering local therapy.

In intra-arterial chemotherapy, medications are injected right into the artery supplying the eye's blood supply. Through intravitreal chemotherapy, drugs are injected directly into the eye. Higher local doses are delivered over the course of a few sessions by these, radiotherapy where cancer cells are destroyed through the use of radiation. One method of administration is to inject radioactive material into the eye, while another method is to direct external beams at the tumor. In the event that other treatments are unsuccessful for treating small tumors, radiotherapy may be utilized as an alternative to surgical procedures for more advanced disease, enucleation which includes the removal of the affected eye through a surgical procedure (Fig 1.3).

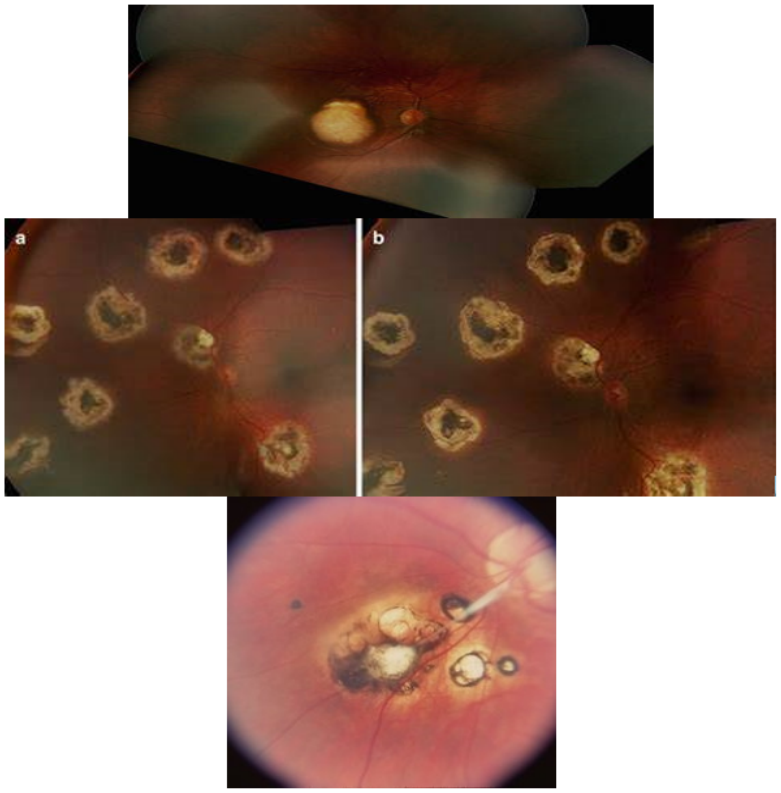


FIGURE 1.3: Retinoblastoma: Focal Therapy – Laser Treatment.

1.2 Epidemiology

Retinoblastoma is the most frequent type of eye cancer in children; however it is still quite rare, affecting about one in every twenty thousand births. The fact that just forty to fifty new cases of retinoblastoma are diagnosed with the condition

each year in the United Kingdom serves as a stark reminder of how uncommon it is. Due to the fact that the current survival rates are commendably around 96%, successful early detection is essential for optimising visual outcomes and quality of life in children who are affected by the condition. However, Rb has the potential to spread to other parts of the body, including the bones, the central nervous system, and the brain. When this occurs, patients typically require intensive chemotherapy for a period of time ranging from months to years after the diagnosis of metastatic disease. Most cases of Rb are diagnosed before the age of five in the United Kingdom, with bilateral presentations typically occurring within the first year and unilateral cases reaching their peak between the ages of 24 and 30 months [8–10]. In countries with lower incomes, the rate of Rb survival is approximately forty percent, whereas in countries with upper-middle incomes, the rate is seventy-nine percent [2, 3, 10].

An emerging excess mortality risk in hereditary cases was brought to light by a study that had 998 Dutch Rb survivors as participants. This finding highlights the necessity of lifelong follow-up. Although screening programmes are beneficial in developed countries, it is possible that they are not adequate in developing nations. This has the potential to have a negative impact on the diagnosis of familial Rb and to increase morbidity and mortality [11, 12]. It is important to note that nurses play a significant role in the detection of Rb, which contributes to the overall survival rates [4, 13].

Factors affecting the prognosis of Rb are the invasion of the optic nerve and the delay in treatment, which highlights the significance of parental awareness and early intervention. Hereditary Rb survivors are at a greater risk of developing a second cancer, which highlights the importance of continuing to monitor them for life [14, 15]. In order to address the challenges of Rb treatment in developing regions, global initiatives are being undertaken by organizations. In the USA, the age-adjusted Rb incidence rate is comparable to that of European countries, and there has been a gradual improvement in 5-year survival over the course of the past 30 years [16–18]. Monitoring for the recurrence of cancer requires that patients undergo post-treatment examinations on a regular basis [19, 20].

1.3 Etiology

Retinoblastoma is an extremely uncommon form of pediatric tumor that originates from the neural tissue of the retina. The development of this trait is further influenced by a significant genetic component. A genetic mutation in the RB1 gene, which is located on chromosome 13, has been linked to the heritable form of retinoblastoma. Chromosomes are the organelles that contain the genetic code that controls the growth and development of cells within the body. There is a possibility that cancer will develop if a portion of this code is removed or changed (mutated). RB1 gene defects can be inherited from a parent or they can develop spontaneously as a result of an error that occurs during the early stages of fetal cell division. It is more likely that inherited retinoblastoma will affect both eyes, and it is also associated with trilateral retinoblastoma that involves the pineal gland, which results in less favorable outcomes [1–3]. There have been a number of different approaches developed in order to identify RB1 mutations and establish a correlation between them and the stage of the disease at the time of diagnosis [3, 5, 9, 21].

A small percentage of patients with retinoblastoma have been found to have a deletion that is located specifically in the 13q14 band on chromosome 13, which led to the discovering of the RB1 locus in this particular region. Microscopic 13q14 deletions, also known as monosomy 13, are present in approximately twenty percent of retinoblastoma tumours. Trisomy 1q and isochromosome 6p are two other cytogenetic findings that are quite common and can be found in a sizeable percentage of tumours. 7 retinoblastoma patients' 10 tumours were analysed for chromosomes, and the results showed that the modal chromosome numbers ranged from 45 to 48. In spite of the fact that the chromosomes were generally stable, there were instances of genome duplications, karyotypic evolution, and random chromosome loss. Trisomy 1q, isochromosome 6p, deletion of 6q, and deletion of 13q12→14 were among the abnormalities that were prevalent throughout the study duration. There is evidence from cytogenetic analysis of patients with bilateral and unilateral retinoblastoma that primary retinoblastoma has a multifocal origin.

Gene amplification that indicated a 1p32 region that was stained uniformly was observed in a tumour that had not been treated, which can be interpreted as evidence of in vivo amplification [20, 22].

1.4 *RB1* Gene and It's Structure

The Retinoblastoma 1 (*RB1*) gene achieved the distinction of being the first tumor suppressor gene to be successfully cloned. The protein that it encodes is responsible for regulating the cell cycle by preventing proliferation. Additionally, it contributes to stable heterochromatin, which helps to maintain the structure of chromatin. There is a connection between the hypophosphorylated form of the protein and the E2F1 transcription factor for interaction. Malignant retinal tumors, such as retinoblastoma, are typically diagnosed based on clinical presentation, and the majority of the time, this occurs in children younger than five years old. Genetic mutations in both *RB1* alleles are necessary for the development of tumors. Sporadic unilateral retinoblastoma is characterized by the spontaneous occurrence of mutations in somatic cells, as opposed to the inheritance of these mutations. However, patients who have sporadic bilateral or familial retinoblastoma are more likely to have *RB1* heterozygosity, which makes them more susceptible to developing the disease.

There is a pattern of inheritance known as autosomal dominant inheritance for familial retinoblastoma. Hereditary retinoblastoma patients, particularly those who have undergone external beam radiation therapy, are at a greater risk of developing extraocular tumors. Variable tumor foci development has been found in carriers of mutant *RB1* alleles, according to genotype-phenotype analyses [23]. This development is influenced by the fact that normal allele functions have been retained. In addition, the phenotypic expression of hereditary retinoblastoma can be altered through genetic modification mechanisms. For the purpose of improving prognosis and suggesting strategies to reduce the risk of tumor development, a comprehensive understanding of these modifying factors may be beneficial [24–27].

It is important to note that the human *RB1* gene contains a total of 27 exons and 26 introns, which contributes to the gene's intricate structure. In accordance with the GenBank accession number NM_000321, it can be found on the long arm of chromosome 13, more specifically at the position 13q14.2. In spite of the fact that the *RB1* DNA has a total length of 178,143 base pairs (bp), it is capable of encoding an mRNA transcript that is 4,772 bp in length and a coding sequence that is 2,787 bp in length. This leads to the formation of a protein that is made up of 928 different amino acids.

In mice, the *RB1* gene can be found on chromosome 14 at 14D3 (GenBank NM_009029). It has a length of 130,238 base pairs in its DNA portion, 4,591 base pairs in its mRNA portion, and 2,766 base pairs in its coding sequence. The production of a protein that is comprised of 921 amino acids is the responsibility of this substance. In a similar manner, the *RB1* gene of chickens is situated on chromosome 1 and possesses a DNA length of 78,217 base pairs, an mRNA length of 4,464 base pairs, and a coding sequence of 2,766 base pairs. It is responsible for producing a protein product that is composed of 921 amino acids (GenBank NM_204419). These genes are responsible for encoding a nuclear phosphoprotein that is 104-110 kilodaltons in size and consists of three domains: the N-terminal domain, the A/B pocket domain, and the C-terminal domain. It is the N-terminal domain that is responsible for providing binding sites for viral and cellular proteins [4]. Figure below is a representation of the *RB1* mutation database, which includes information regarding the structural characteristics of the *RB1* gene (Fig 1.4) [2, 28–31].

1.5 *RB1* Gene Function

The *RB1* gene is a significant tumor suppressor that can prevent certain malignancies, such as osteosarcoma, breast, pancreatic, small cell lung, and retinoblastoma. Numerous studies have demonstrated the close relationships between the *RB1* tumor suppressor and critical biological functions, including differentiation, ageing, apoptosis, growth inhibition, and cell cycle regulation [32, 33].

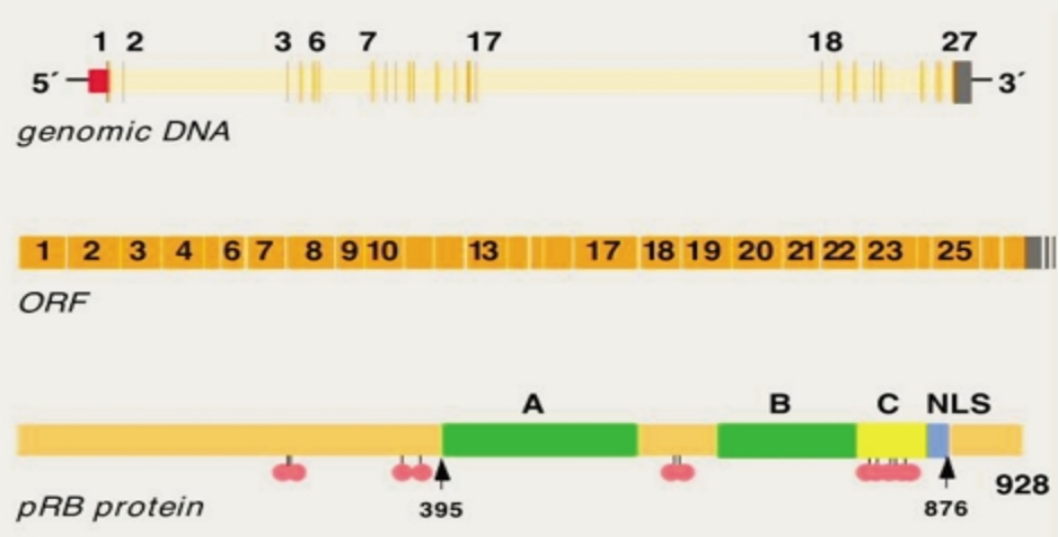


FIGURE 1.4: *RB1* Gene Structure.

As a negative cell cycle regulator, *RB1* mainly stops cancer from spreading by attaching to E2F. As a result, the cell cycle stops short of passing through the G1-S checkpoint and comes to an end. In order to control gene expression, which is necessary for cell differentiation across tissues, the active form of pRB collaborates with transcription factors that are particular to distinct tissues. This emphasizes how important *RB1* is for controlling proliferation and differentiation [2, 3, 9].

1.6 Causes

RB1 genetic changes, which are present in every single cell in the body, including cells that are responsible for reproduction, are estimated to be responsible for approximately one-third of all cases of hereditary retinoblastoma, according to the findings of investigators. Hereditary retinoblastoma patients have a higher likelihood of passing on the mutant *RB1* gene to their offspring than those who do not have the disease. A single mutant copy in each and every cell is sufficient to increase the likelihood of developing cancer. This is due to the fact that *RB1* abnormalities in inherited cases follow an autosomal dominant pattern from generation to generation. It's possible that the altered gene was caused by a recent mutation, or it could have been passed down from a parent [34].

The other three quarters of retinoblastomas are rarely inherited. This is due to the fact that *RB1* abnormalities are restricted to retinal cells and are not transmitted. Individuals who are born with non-hereditary retinoblastoma have two copies of *RB1* that are normal. There are certain retinal cells that, throughout the early stages of life, undergo mutations in both copies. Patients with non-hereditary retinoblastoma do not face the risk of passing on these genetic variants to their offspring, in contrast to patients with hereditary retinoblastoma. In order to differentiate between genetic and non-hereditary types, statistical analysis of genetic material is frequently required [35–37].

1.7 Mutations

RB1 gene variants are the most common cause of retinoblastoma, which is a potentially fatal cancer. In addition to its function as a tumor suppressor, the *RB1* gene is an essential component in the process of monitoring the growth of cells and preventing excessive or uncontrolled sub cellular division. In patients who have been diagnosed with retinoblastoma, the majority of mutations that occur in the *RB1* gene hinder the gene's ability to produce a protein that is functional. It is as a consequence of this that the cells that are affected lose their capacity to effectively regulate cell division. This malfunction makes it possible for certain cells in the retina to undergo division that is not under control, which ultimately leads to the development of tumors that are affected by cancer (Fig 1.5) [38].

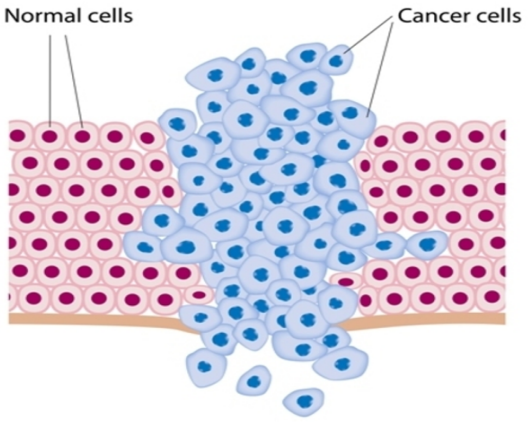


FIGURE 1.5: Mutation in cells.

Retinoblastoma can result from various forms of mutations, primarily affecting the *RB1* gene. These mutations can be classified into the following categories, which are more general in nature:

1.7.1 Point Mutations

1.7.1.1 Missense Mutations

Mutations known as missense mutations are characterized by the presence of a single nucleotide change that transforms the sequence of amino acids that are present in the resulting protein. The retinoblastoma protein may be dysfunctional as a consequence of a missense mutation that is associated with the *RB1* gene.

1.7.1.2 Nonsense Mutations

Nonsense Mutations: In this particular instance, a point mutation causes the introduction of an early stop codon, which in turn truncates the synthesis of the protein. In most cases, the protein that is produced is either completely dysfunctional or severely impaired.

1.7.1.3 Insertions and Deletions (Indels)

These mutations involve the insertion or deletion of nucleotides, which results in frameshift, which is the process of reading frames during reading frame during translation. As a consequence of this mutation, the protein that is produced is frequently either shortened or rendered irrelevant.

1.7.1.4 Splice Acceptor or Donor Site Mutations

Changes in the regions that determine the splicing of introns during the processing of mRNA can result in aberrant splicing patterns. These mutations can occur at either the splice acceptor or the donor site. As a result, this could result in

the inclusion of incorrect exons or the exclusion of essential exons, which would ultimately have an impact on the operational capabilities of the protein.

In this particular instance, a particular kind of mutation known as a point mutation causes the insertion of an early stop codon, which ultimately results in the production of the protein being shortened. In the majority of cases, the protein that is produced is either completely devoid of any functional properties or significantly impaired.

1.7.2 Large Deletions or Duplications

1.7.2.1 Deletions from the Chromosomes

RB1 gene deletions on a large scale have the potential to cause the gene's function to be reduced or eliminated entirely. It is possible for this kind of mutation to have an effect on multiple exons and to cause structural disruptions in the retinoblastoma protein.

1.7.2.2 Chromosome Duplications

It is possible for there to be instances in which chromosomal segments, including the RB1 gene, are duplicated simultaneously. Consequently, this could result in an over expression of the retinoblastoma protein, which could potentially have an effect on the regulation of the cell cycle.

1.8 Problem Statement

Retinoblastoma is a malignant tumor of retina affecting the young children. Identification of genes involved in development and progression of retinoblastoma remains a challenging task due to the complexity of genetic interaction and extensive amount of genomic data. Understanding of genetic basis of retinoblastoma is essential for early diagnosis, improved prognosis and effective treatment.

1.9 Aim and Objectives

The aim of this study is to predict and analyze the genes associated with retinoblastoma.

- To predict genes associated with retinoblastoma using text mining
- To perform functional annotation of retinoblastoma-associated predicted genes
- To explore the involvement of predicted genes in retinoblastoma-related pathways
- To validate the cluster protein's interactions

Chapter 2

Literature Review

One kind of malignant tumor that affects the retina's developing cells—the ones that give rise to the sensation of light—is called retinoblastoma [39]. Only newborns and young children are most likely to be affected by this extremely rare kind of cancer. However, the majority of children do survive this sickness, albeit with some complications. There is a possibility that severe consequences will occur, such as the removal of the eye or complete blindness in the eye that is affected.

2.1 Diagnosis

In accordance with the guidelines, treatment and care should be provided to young children and families who have been affected by retinoblastoma [40]. It is essential to ascertain the extent of the tumor or the degree of its severity before beginning the process of formulating a treatment plan. Following the determination of the size of the tumor and the likelihood that it will spread, a particular stage of cancer is assigned to the patient [41]. In the diagnosis of retinoblastoma, MRI and tomography are the method of choice.

- The term "MRI" stands for "Magnetic Resonance Imaging," which that makes availability of magnetic fields to produce images of the internal organs of the body that are extremely detailed. When determining the size of tumors that are affecting the optic nerve, it is helpful to have this information [42]

- It is generally not recommended to undergo CT scans because of the presence of radiation, which has the potential to result in the development of secondary cancers

- For the purpose of early detection of small tumors that may exhibit symptoms such as strabismus and changes in eye appearance, tomography is utilized in individuals who have a family history of retinoblastoma [43]

2.1.1 Establishing the Diagnosis

An examination of the proband's retina and an evaluation of the pupil's dilation are the two methods that an ophthalmologist uses to diagnose retinoblastoma in a proband. Through anesthesia analysis, both the confirmation of the diagnosis and the evaluation of the severity of the disease can be accomplished. There is a possibility that retinal scanning could be highly effective in establishing the correct diagnosis.

In most cases, retinoblastoma is diagnosed at an earlier stage in individuals who come from families that have a genetic predisposition to experiencing the disease. However, the great majority of individuals with retinoblastoma do not have a family history of the condition. For these patients, molecular genetic testing must identify a pathogenic heterozygous germline Rb1 to determine whether or not the retinoblastoma is inherited. Early detection and screening of retinoblastoma risk in the affected individual's relatives is made possible through the identification of a disease-causing variant of the Rb1 gene in the affected individual with the disease.

For the purpose of elucidating the genetic risk that is associated with a pathogenic variant of germline Rb1, it was suggested that the following staging be utilized [41].

HX: The individual with a documented genetic mutation in the Rb1 gene, which is inherited and affects all cells of the body, is referred to as HX. However, the evidence that supports this mutation is either unknown or insufficient.

H0: Individuals diagnosed with retinoblastoma who have been confirmed by molecular genetic testing to have an unknown germline Rb1 pathogenic variant.

H0*: This is a reference to patients who have been diagnosed with retinoblastoma but who, according to the results of molecular genetic testing, do not have a known pathogenic Rb1 germline variant.

H1: People who have a history of retinoblastoma in their family, a pathogenic form of Rb1 germline, or bilateral or trilateral retinoblastoma are at risk for developing this condition.

2.2 Signs and Symptoms

An association should be made between retinoblastoma and the following symptoms in children. A condition known as leukocoria, also referred to as a white pupil, is characterized by the appearance of the pupil as being white rather than its typical color. Strabismus, as it is more commonly known, is a condition in which the eyes are not aligned correctly and do not look in the same direction. Strabismus is also commonly referred to as crossed eyes. A change in the appearance of the eyes and a reduction in the ability to see clearly. Through the use of complete pupillary dilation, an ophthalmologist or optometrist can confirm the diagnosis of retinoblastoma in a patient, who is referred to as a proband. An evaluation of the severity of the disease as well as the confirmed diagnoses are carried out while the patient is under anesthesia.

In order to confirm the diagnosis, ophthalmic imaging is administered. Clinical pathology is not required. It is generally not recommended to perform a biopsy because of the possibility of the tumor spreading to other parts of the body and the associated danger to the individual's life. Individuals who have a history of retinoblastoma in their family should be evaluated for the possibility of having hereditary retinoblastoma. The diagnosis should take into account the presence of retinoma, the number of tumors, whether they are located in a single location or multiple locations, and the presence of tumors on both sides as well as on

one side. Additionally, the diagnosis should take into account the presence of tumors on both sides. Heritable retinoblastoma can be identified through the diagnosis of retinoma in individuals, as well as in those who have a history of retinoblastoma in their family. On the other hand, the vast majority of people who have retinoblastoma do not have a family history of susceptibility to this condition. It is necessary for these patients to undergo molecular genetic testing in order to identify a pathogenic heterozygous germline Rb1 mutation [39]. This will allow for the determination of whether or not the retinoblastoma is inherited.

2.3 Nature of Disease

2.3.1 Unilateral

When it only affects one eye, retinoblastoma is referred to as a unilateral form of the disease. Twenty-four months is the typical age at which a diagnosis of unilateral retinoblastoma is confirmed. It is estimated that approximately sixty percent of people who have retinoblastoma only have the condition affecting one eye. Individuals who suffer from unilateral conditions typically also have a single tumor that is unifocal in characteristics. A single retinoblastoma tumor can be seen in this patient. There are some people who can develop multiple tumors within a single eye during their lifetime. Through the use of intraocular seeding, it is possible to simulate the development of secondary tumors. The majority of people who have sporadic unilateral retinoblastoma are affected by the disease tumors that are typically quite large in size are typically present.

2.3.2 Bilateral

Individuals who are diagnosed with bilateral retinoblastoma are those who have the condition in both of their eyes. Around 40% of people have tumors in both eyes, and the average age at which retinoblastoma is diagnosed is somewhere around fifteen months.

The majority of children are thought to be affected by the condition known as bilateral, which typically affects both eyes. Neoplasms that were discovered during the preliminary diagnosis. Multiple tumors may be present in both eyes of individuals who have been diagnosed with bilateral retinoblastoma. There is a possibility that people who initially have tumors in one eye may later develop tumors in the other eye as well. This is a possibility.

2.3.3 Trilateral

When there is a presence of both bilateral retinoblastoma and the subsequent development of pinealoblastoma, this condition is referred to as trilateral. The specific condition in question is referred to by this term [39]. A pinealoblastoma is a type of tumor that develops in the pineal gland of the brain, more specifically in tissue that is similar to but not identical to the retina. In the case of trilateral retinoblastoma, both pinealoblastomas and retinoblastoma are present during the course of the disease. However, in contrast to eye retinoblastoma, which is typically treatable, pinealoblastoma is an extremely uncommon and typically fatal condition [44]. Pinealoblastoma is a condition that is typically fatal.

2.3.4 Other Types of Tumors

There are additional instances of secondary tumors that are of a significant size and have a higher probability of developing. On the other hand, the majority of second primary tumors are osteosarcomas, which are a subtype of soft tissue sarcoma that primarily affects the bones [45–47].

When individuals with retinoblastoma have received treatments such as external radiation therapy, the incidence of second primary tumors is significantly increased, reaching nearly fifty percent [32]. This is a significant increase from the previous incidence. The likelihood of developing secondary cancers is significantly increased in patients who have hereditary retinoblastoma. Those individuals who have not yet been subjected to a substantial amount of radiation therapy [47–50].

2.4 Types of Retinoblastoma

The two types retinoblastoma are 1) Hereditary: The inheritance of hereditary characteristics can occur within families and 2) Sporadic: Occurring in a sporadic manner and not being passed down through extended families.

2.4.1 Hereditary

A heritable form refers to a condition in which there is a documented family history of the disease. In these cases, tumors are predominantly found in both eyes, known as bilateral, or occasionally in just one eye [51].

2.4.2 Sporadic

A condition that is not inherited and is characterized by the absence of any history of the disease in the patient's entire family. The term "unilateral" refers to the fact that tumors typically only affect one eye. RB affects approximately 55 percent of children [42], which is a significant proportion.

2.4.3 Groups of Classification

Patients who have been diagnosed with retinoblastoma are classified in accordance with the Reese Ellworth classification, which can be found below in table 2.1 [52].

TABLE 2.1: Classification of people diagnosed with retinoblastoma according to Reese Ellworth

Groups	**Descriptor**
Group A	• It is possible to define a tumor as a unifocal tumor if it has a diameter of less than four centimeters and is situated either at the equator or behind it.

Table 2.1: Classification of people diagnosed (Continued).

Groups	**Descriptor**
	• In the event that there is a tumor that affects multiple focal points, the size of the tumor should not be greater than four discs in diameter. It is recommended that all entities be situated either directly on the equator or to the rear of those points.
Group B	• In the event that the tumor is unifocal, its diameter ought to be somewhere in the range of four to ten. There is a possibility that the tumor is situated either on or behind the equator.
	• If there is a tumor that affects numerous sections of the eye, it should be located behind the equator of the eye.
Group C	• The lesion can be found on the side of the equator that is in front of the body.
	• Tumors those are isolated and greater than ten discs in diameter. The majority of its location is south of the equator.
Group D	• The location of the lesion is considered to be on the frontal aspect of the equator.
	• Tumors that are positioned in a single area and have a diameter that is greater than three discs with the majority of its territory being in the southern hemisphere.
Group E	• Fifty percent of the retina is damaged by cancerous areas.
	• A process that involves the spread of cells or particles throughout the vitreous fluid of the eye.

2.5 Genetics

2.5.1 MYCN

MYCN is a gene that belongs to the MYC family of proto-oncogenes. It is classed as a member of this family. The transcription factor known as MYCN plays a

function in the regulation of significant processes that occur during the embryonic development process. When it comes tosignaling pathways, the MYCN protein is located downstream of many of them. Pathways that are responsible for facilitating the growth, proliferation, and metabolism of progenitor cells in various organs and tissues that are in the process of developing. Unregulated MYCN signaling, on the other hand, is responsible for the proliferation of certain types of cancers, particularly those that occur in early childhood. These cancers include neuroblastoma and retinoblastoma.

2.5.2 *Rb1*

The gene known as *Rb1* gene is the first gene to be identified as a tumor suppressor. The size of the gene is quite substantial, since it is 190 kilobases in length and is composed of 27 exons. This gene is accountable for the encoding of a messenger RNA (mRNA) molecule that is 4.7 kilobases in length. This mRNA molecule, in turn, plays a role in the translation of proteins that are composed of 928 amino acids [53]. As a tumor suppressor, the *Rb1* gene, which may be found on chromosome 13q14, is responsible for its function. This particular gene is accountable for the production of a nuclear phosphoprotein that is referred to as pRb. During the course of the cell cycle, the process that is known as checkpoints is responsible for regulating the transition of cells from the G-phase to the S-phase [54].

2.5.3 Mutation in *Rb1* and Amplification of MYCN

Alterations such as point mutations, promoter methylation, and indel mutations are examples of the kinds of changes that can have an effect on the functioning of pRb. The majority of the time, pRb is classified as a controller of the cell cycle, specifically in terms of its ability to regulate the process of cell division. After some time has passed, it makes a connection with E2F transcription factors, which inhibits the production of genes that are important in the proliferation of cells. Cycline dependant kinases (CDKs) are responsible for the hyperphosphorylation of pRb, which occurs when mitogenic signals are received.

Repression is frequently alleviated as a result of this process, which also makes the transition from the G1 phase to the S phase easier. As a result of the lack of pRb, the cell cycle is able to continue even when mitogenic stimuli are not present, which prevents the crackdown from occurring. It is possible to postulate that pRb plays a significant part in suppressing E2F transcription factors, and that the failure of this function is the fundamental mechanism that leads to the development of retinoblastoma [55]. In addition to the amplification of MYCN oncogenes, there are a number of other causes that have been discovered for the non-inactivation of *Rb1*. Recently, it has been discovered that patients who have been diagnosed with RB have a lesion [56].

There have been two separate instances in which mutations have been found in exon 20 of the Rb1 gene. When a C——T transformation takes place at the 661st codon, which results in the conversion of an arginine (CGG) to tryptophan (TGG), this is an example of a specific point mutation that can be noticed [54].

Almost all patients are observed to have limited penetration and a mild phenotypic manifestation, which is a common observation. A proposition that suggests that changes in the shape and function of proteins can be brought about by alterations in individual amino acids. Codon 675 has been shown to contain a mutation in another instance of the disease. The glutamine (GAA) is converted into a stop codon (TAA) as a result of the transition that takes place through the G——T.

2.6 Protein Associated with Retinoblastoma

As a protein, *Rb1* has been associated with retinoblastoma. It is found in a wide variety of healthy cells and does not cause any significant changes in the regulation of the cell cycle. Both cellular proliferation and differentiation are intricate processes that are influenced by a wide variety of different factors.

There are a number of variables that are involved in these processes, and these factors have the ability to control how those variables are expressed. There is a distinct and one-of-a-kind expression pattern of *Rb1* that is consistent across

all tissues and stages of development. It is possible to observe variations in the pattern across the various types of tissues [2, 5, 7].

There are 928 different amino acids that make up Rb1, and its molecular weight is 106,159 Daltons. It is the composition of the object that leads to the determination of its size. When *Rb1* interacts with ATAD5, it does so through a process that is referred to as similarity. This serves as an example of an interaction that occurs between one subunit and another [57, 58].

It is during this process that the Rb1 protein, which has a low level of phosphorylation, interacts with the E2F1 transcription factor, which ultimately results in the transcription factor being sequestered. According to the particular combination, this protein is involved in the formation of complexes with TFDP1 and E2F1, E2F3, E2F4, or E2F5, or TFDP2 and E2F4, depending on the specific protein combination [1]. Furthermore, the unphosphorylated form of *Rb1* has the ability to bind to a wide variety of other proteins, including AATF, DNMT1, LIN9, LMNA, SUV420H1, SUV420H2, PELP1, TMPO-alpha, NDC80, GRIP1, UBR4, ARID4A, KDM5B, E4F1, LIMD1, SMARCA4/BRG1, HDAC1, adenovirus E1A protein, HPV E7 protein, SV40 large T antigen, PSMA3, and USP4 (Table 2.2) (as mentioned in references [42, 54].

TABLE 2.2: Interacting Proteins for *Rb1*

***Rb1* Genes**	**Interacting proteins**
E2F1	EBI-491274, EBI-448924, MINT-1777462, MINT-4793606, MINT-1777305, MINT-4793665, MINT-73329, MINT-4793592, STRING: ENSP00000345571
HDAC1	EBI-491274, EBI-301834, MINT-73395, MINT-6628404, MINT-77956, STRING: ENSP00000362649
E2F2	MINT-4793621, MINT-4793646, STRING: ENSP00000355249
MDM2	MINT-1776635, STRING: ENSP00000258149
TAF1	EBI-491274,EBI-491289, STRING: ENSP00000276072

The retinoblastoma susceptibility protein Rb is responsible for a significant part of the regulation of the progression of the cell cycle. This is accomplished through interactions between its central "pocket" region and its C-terminus. It has been found that the conserved N-terminal domain contains missense mutations that are associated with hereditary retinoblastoma. This finding suggests that the domain plays a significant role in the process of development, despite the fact that it is not essential. Due to the presence of a spherical fold that is produced by two cyclin-like repeat groups, the crystal structure of the N-terminal domain (RbN) provides evidence that Rb may have evolved through the process of domain duplication. An in-depth investigation into the structure and function of the protein leads to the discovery of a location where phosphorylation is responsible for regulating the interaction between proteins. In addition to this, it sheds light on the potential for RbN mutations to cause cancer. Moreover, this investigation suggests a consistent arrangement for the entire Rb protein, in which the RbN region and the pocket domain directly interact with each other and can be affected by ligand binding and possibly Rb phosphorylation [57–59]. This arrangement is consistent with the findings of the previous investigation.

It is possible for a cancerous tumor of the retina known as retinalblastoma (Rb) to develop in either one eye or both eyes, or it can develop unilaterally, meaning that it could only affect one eye. Rb is typically considered to be localized within the eye, and in the majority of cases, it does not spread to other tissues. Rb treatment presents a number of challenges, the most significant of which is the prevention of vision loss and the mitigation of potential severe treatment-related side effects, which may have an effect on overall quality of life as well as lifespan. A hereditary or germline nature is responsible for approximately forty percent of all cases [2, 39, 59]. The region of chromosome 13q14 is where the genetic locus that is associated with retinoblastoma (Rb) predisposition can be found. The risk of developing secondary cancers is significantly increased in people who have Rb, particularly those who have the inherited form of the disease. On the basis of the clinical manifestations of the condition, Rb is typically diagnosed in children who are younger than five years old. There is a requirement for the presence of biallelic mutations in the RB1 gene in order for Rb to manifest [4]. A detailed summary

of the epidemiology of Rb and the RB1 gene is presented in Table 2.2, which can be found here. References [2, 3, 7, 53, 56] are included in this document.

Both of the RB1 mutations that are found in cases of sporadic unilateral retinoblastoma are typically acquired somatically and are not passed down through families. However, hereditary heterozygous *RB1* mutations are the cause of the majority of cases of sporadic bilateral retinoblastoma and nearly all familial cases. These mutations raise the risk of developing retinoblastoma in children. A pattern of inheritance known as autosomal dominant inheritance is responsible for the transmission of familial Rb predisposition [2, 7, 14].

To add insult to injury, people who have hereditary retinoblastoma have a higher risk of developing secondary cancer, which is a type of cancer that occurs in other parts of the body. In particular, this is true after having previously undergone radiation therapy with an external beam. Genotype-phenotype associations demonstrate that individuals with mutant *Rb1* alleles develop tumor foci in a variety of different ways, depending on the functions that are maintained by the normal allele.

Modifications to genetic material have the potential to affect the way in which hereditary retinoblastoma characteristics manifest themselves. Not only does the identification of the genetic factors involved improve the accuracy of the prognosis, but it also provides valuable knowledge that can be utilized to develop strategies that are aimed at reducing the risk of tumor development in patients.

2.7 Genetic Counseling

Genetic counseling is a process that assists families in comprehending the characteristics of genetic anomalies, including their inheritance status and the implications of these abnormalities. It offers information that can be used to assist in making judgments on personal choices and individual medical treatments. The autosomal dominant inheritance pattern is the one that is responsible for heritable retinoblastoma. The dangers that members of the family face are as follows:

2.7.1 Parents of Affected Individual

- In the event that an individual has inherited a mutation in the Rb1 gene from their parents, who may or may not be affected by retinoblastoma, there is a possibility that the individual developed the disease. In approximately five percent of cases, there is only one person who is affected by the condition.

- It has been determined that the individual in question possesses a genetic mutation in the Rb1 gene, which is found in their reproductive cells. However, despite having a pathogenic variant, the parent does not exhibit any symptoms of retinoblastoma disease because they do not have the disease themselves. Reduction in penetrance or missense variants are the terms used to describe these kinds of cases.

- Hereditary retinoblastoma can be caused by denovo mutations, which occur in the germ cell during the process of fertilization. These sorts of mutations can be passed down through generations. On the other hand, neither of the individual's parents possesses this variation, and there is no previous history of retinoblastoma throughout the family. In these kinds of situations, it is recommended to carry out molecular genetic testing on both the parents and the individual who is struggling with the condition. The variation can be identified in both the probe and the parents via either sanger sequencing or next generation sequencing [60].

- As a result of the failure to diagnose retinoblastoma in the probe's family and the presence of heritable retinoblastoma, it is not possible to confirm that the individual being examined does not have a family history of retinoblastoma until genetic testing is performed on the parents of the individual being examined. Among the members of the family, there is a possibility of decreased penetrance.

- When the probe is found to contain somatic *Rb1* mutations, it indicates that the proband's parents do not have any variations in their genes. This means that the mutation is not inherited from the parents.

2.7.2 Risk to Siblings of Affected Individual

Both the genetic and phenotypic characteristics of the probe and the parents will determine the level of risk that is posed to the siblings.

2.7.2.1 Parents Phenotype

- The risk of developing retinoblastoma is 50% for siblings of a proband who have bilateral retinoblastoma along with their parents for developing the disease themselves.
- The risk to siblings is lowered to between 1% and 2% in the event of low penetrance, which occurs when parents frequently do not exhibit clinical symptoms. There is still a possibility that individuals will develop retinoblastoma.

2.7.2.2 Parents Genetic Status

- If both parents have heterozygous pathogenic variants of *Rb1*, then both probe and parent are affected, and there is a 50% chance of affected siblings.
- This means that the possibility of the sibling being harmed is <5% in case the penetrance is diminished. Even so, it is still recommended to conduct a test on the sibling to determine whether or not the probe has a de novo inherited mutation. If this particular mutation is not discovered in the siblings of this individual, such siblings are unaffected [61–63].
- When a somatic Rb1 mutation is present in the probe, the likelihood that a sibling may be affected by the mutation is greatly reduced.

2.7.2.3 Risk to Proband Offspring

- If a person has bilateral retinoblastoma but there is no history of the disorder in their family, they are considered to be H1 cases and have a fifty percent chance of passing on the mutation to their children [63].

- If an individual has many cancers but there is no history of these tumours in their family, the risk of these tumours being passed on to their children is significantly reduced.
- There is a possibility of getting retinoblastoma in approximately six percent of the kids of a proband who has unilateral unifocal retinoblastoma and who does not have a history of the disease in their family background [64].
- There is a lack of clarity on the level of germline involvement in cases where the proband has a positive family history of retinoblastoma. Given that the descendants have a higher risk of developing cancer, it is of the utmost importance to do a thorough examination of each and every one of them for the presence of the mutation.

2.7.2.4 Genotype/Phenotype Correlation

- The condition hereditary retinoblastoma is distinguished by the transmission of germline mutations to offspring, which ultimately leads to the development of multifocal bilateral tumours that are completely penetrating [65–67].
- It is estimated that approximately ten percent of families have incomplete penetrance, which is brought on by missense mutations.
- You could also have a variation or mutation at the splice site or promoter area. In particular families, the degree of disease manifestation may differ depending on maternal or paternal inheritance of pathogenic gene.
- The indel mutations of chromosome 13 is associated with developmental delays and dysmorphism, according to a study that investigated the inheritance of chromosomes.

2.8 Management

All of the management tactics that are described below are put into action.

- Children who are under the age of one and who are suspected of having retinoblastoma should have their eyes examined every three to four weeks while they are under anaesthesia. Keeping up with the routine examinations in this manner is something that should be prioritised. The average age at which infants start walking is somewhere about six months of age. After that, reduce the number of clinical examinations that the child has to once every six to three months until the child reaches the age of three to seven years. The number of checkups that were performed was eventually decreased to once a year [61].

- One type of retinoblastoma is known as sporadic retinoblastoma, which is a form of the disease that does not inherit and appears at random. It is recommended that those who have unilateral vision impairment undergo routine eye examinations, which should include ocular imaging and ultrasonography. Due to the fact that there is a chance of developing a cancer in the eye that is not affected, this is a significant consideration [68].

- A retinal examination and an ultrasonography examination are frequently performed on patients who have been diagnosed with retinoma [68].

- The increased likelihood of acquiring secondary cancers makes it prudent to undergo whole-body magnetic resonance imaging (MRI) scans on a frequent basis for the purpose of early detection [39]. By reducing the amount of harmful substances that H1 RB survivors are exposed to, it is possible to reduce the likelihood that they may get cancer. A No. of different forms of radiation, smoking, and ultraviolet light can all have an effect on DNA [45].

- It is inherited in an autosomal dominant pattern. Individuals who have been diagnosed with hereditary retinoblastoma (H1) have a harmful mutation in their *Rb1* gene. There is a 50% chance that the harmful mutation will be passed down to the offspring of H1 individuals.

In the event that a member of the family who is affected has been identified as having the Rb1 pathogenic variant, it is feasible to carry out prenatal testing for pregnancies that are at a higher risk.

Chapter 3

Material and Method

3.1 Retrieval of Genes Related to Retinoblastoma by Using COREMINE

Using the firm's one-of-a-kind text mining algorithms and vast biomedical data integration and analysis pipeline, the Norwegian bioinformatics company PubGene developed a suite of tools known as COREMINETM. These products were built by the company.

On top of the COREMINE Platform, Coremine MedicalTM is the first information community tailored to a particular domain. This is a free Internet service that allows users to search for, update, and share medical information online. It functions as both a search engine and a social network https://coremine.com/medical/.

When it comes to text mining, having access to material on the proper topic is absolutely necessary [16]. The principal source, the PubMed database, provides access to this information in the form of a published corpus about retinoblastoma in the field of biomedical literature [17].

The MeSH database was searched for the MeSH main topic "retinoblastoma" for the purpose of retrieving genes related to retinoblastoma. A collection of texts that were published during the last ten years i.e. 2014 to 2024 was gathered.

Retrieving literature published within the last 10 years ensures access to up-to-date information, which is crucial for informing and advancing scientific understanding in the field of retinoblastoma.

By searching for both MeSH major topics and specific terms, the retrieved literature is highly relevant to the topic of interest, minimizing irrelevant results and optimizing the effectiveness of text mining efforts.

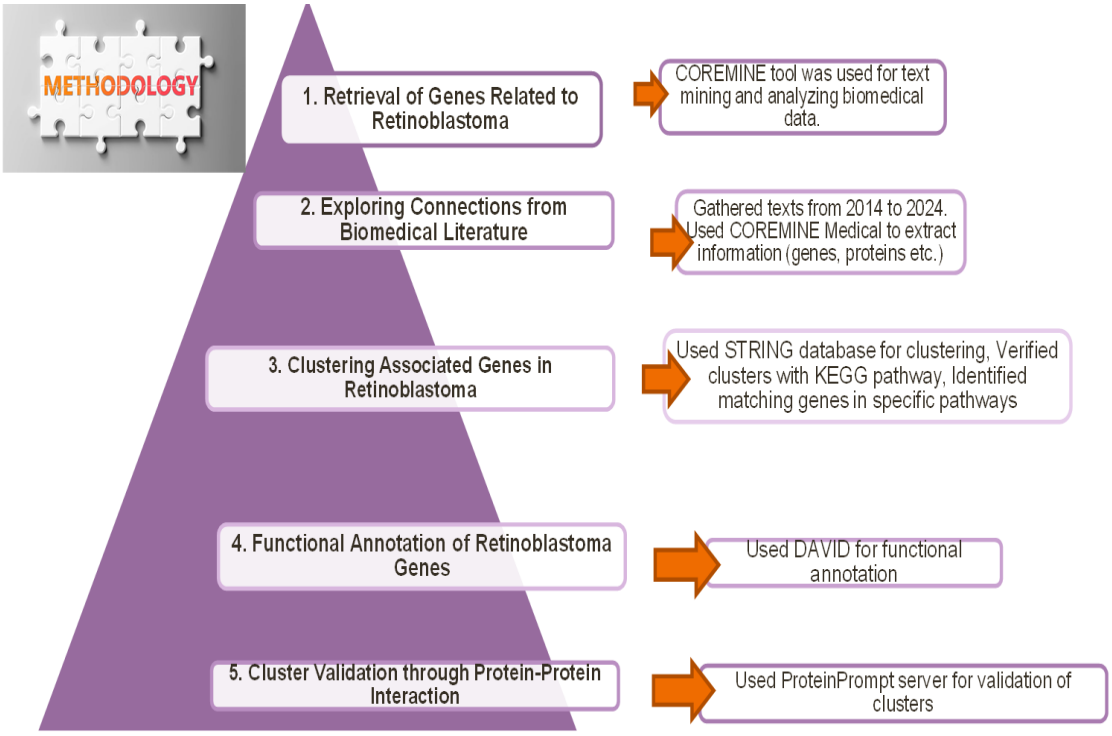


FIGURE 3.1: Methodology flowchart.

3.2 Exploring Connections from Biomedical Literature

When it comes to analyzing text in the biomedical literature, there is a variety of tools available. A biomedical text mining technology called COREMINE medical was used in order to extract a variety of information from the published scholarly works. This information included genes, proteins, MeSH terms, processes, ailments, and drugs. Downloaded in a text document were the results that were discovered.

3.3 Clustering of Genes in Retinoblastoma Using STRING and Verification by KEGG

Clustering is a technique used in data mining and machine learning to group together data points that are similar to each other based on specific properties. Creating a condition where the data points within each cluster are more comparable to each other than the data points within other clusters is one of the objectives when dividing a dataset into subsets or clusters. Several different clustering techniques, including K-means, hierarchical clustering, and DBSCAN, are used to automatically find these groupings [69, 70].

Clustering was done using STRING database. After that KEGG pathway was utilized to verify clusters generated while working with STRING database. The KEGG pathway comprised 38 retinoblastoma pathways. In all 38 pathways, we verified clusters ranging from 3 to 25, as obtained from the STRING database. We identified matching genes in the following pathways:

The fourth pathway, known as Pathways in cancer, is associated with Cluster number 4, which is referred to as FH. Similarly, the seventeenth pathway, named Cushing syndrome, is also linked to Cluster number 4, FH. Lastly, the thirty-fourth pathway, called transcriptional misregulation in cancer, is associated with Cluster number 20, FUT8.

Remaining genes i.e. *DAZAP1, HOXA1, HOXA9, HOXB2, HOXB5, HOXC9, MAB21L1, MEIS1, MSI2, NUP107, NUP205, NUP62, NUP98, NXT1 , PBX1 , PBX3, PCDH17, ACACB, ACLY ,COASY , CPT1B, ELOVL6 , FASN , IDH1, MLYCD , NSDHL , PDHX , SCAP, SLC25A1 , SUCLA2 , TWNK, ABCC1, ABCC2 ,ABCC3 ,ABCC4 ABCG2, SLC22A3, SLC22A5, SLC44A5, SLC47A1, SLCO4A1, ABCA4, CNGB1, EYS, PDE6C, ROM1, RS1, SLC24A2, DDX1, FAM98B, LRRC39, RTCA, RTCB, RTRAF, SLC1A5, SLC43A1, SLC6A15, CRX, ZACN, CEL, LIPA, NPC2 ,PNPLA2, PNPLA3, CSMD3, EXT1, FAT3, LRP1B, ARR3, CLUL1, SLC7A5, RBP3, HFM1, SLC39A1, SLC39A5, GPRIN2, HYDIN, NPY4R, SLC7A13, SLC7A14, SLC7A4, CAT, RGN, TSTD1, TARS1, TARS2,*

TARS3, CHCHD2, CHCHD3, CHCHD6, APOBEC3A, APOBEC3B, CASC1, DNAH8, FUT3, ADGRL4, MYCT1, CIB2, PCDH15, EL-FN1, ELFN2, CDO1, SLC6A6, SLC13A5, SLC15A5 were all predicted genes Table 3.1.

TABLE 3.1: Observing matching genes (already reported) in KEGG RB pathways and Clusters

Pathway No.	**Pathway Name**	**Cluster No.**	**Genes in Cluster**
4	Pathway in cancer	Cluster no 4	*FH*
17	Cushing Syndrome	Cluster no 4	*FH*
34	Transcriptional misregulation in cancer	Cluster no 20	*FUT8*

3.4 Functional Annotation of Retinoblastoma Genes by DAVID

The predicted genes were functionally annotated using DAVID. An established web server and web service for functional annotation of gene lists are part of the bioinformatics resource system DAVID. It comes with a sizable knowledge base and a number of functional analysis tools [71]. DAVID was performed after a list of predicted genes was uploaded. Since these genes are found in humans, Homosapiens species were chosen. A collection of settings is required to operate the DAVID gene ontology. The most stringent categorization criterion was chosen in order to efficiently screen the retinoblastoma genes' functions.

3.5 Cluster Validation Through PPI

The physical contacts formed between two or more proteins are known as protein-protein interactions (PPIs), and they are essential for a number of biological activities that occur within cells. In addition to numerous other cellular processes,

these interactions are essential for signal transduction, enzyme activity regulation, and cellular transport. The ProteinPrompt server is an internet-based bioinformatics tool utilized for the prediction and analysis of protein-protein interactions. Researchers utilize this method to verify the functional significance of proteins by detecting and verifying their interactions with other proteins in different biological pathways. This server is highly valuable for investigating intricate biological processes and comprehending the molecular pathways that underlie different disorders [72].

The FASTA sequences of proteins ranging from cluster 3 to cluster 25 were sequentially inputted into the ProteinPrompt server (https://proteinformatics.uni-leipzig.de/ProteinPrompt/). The server provided the result in a tabular format consisting of 999 entries. Next, we conducted a search for proteins that were found in our clusters and also appeared in the ProteinPrompt tabular output. The server tabular result indicated the presence of proteins from cluster 3 and cluster 11. Consequently, these clusters were validated using Protein-Protein Interaction (PPI) analysis. Version 2.0 of the ProteinPrompt server was utilized for this purpose

Chapter 4

Results

4.1 Retrieval of Genes by COREMINE

The initial stage was extracting genes using the COREMINE tool. This was accomplished by accessing the search bar of the tool and conducting a search for the specific disease, retinoblastoma. After selecting the "extracted associations" option in the COREMINE interface, we proceeded to extract the associations spanning from the year 2014 to 2024. COREMINE generated a list of 2000 genes associated with retinoblastoma when the query "Retinoblastoma (Genes/Proteins)" was used. A comprehensive Excel spreadsheet with the names of the corresponding genes, disorders, and their respective descriptions was acquired (Table 4.1).

Table 4.1: List of genes of retinoblastoma.

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1	Retinoblastoma	*RB1*	Gene/Protein
2	Retinoblastoma	*RBL1*	Gene/Protein
3	Retinoblastoma	*CDK4*	Gene/Protein
4	Retinoblastoma	*RBL2*	Gene/Protein
5	Retinoblastoma	*E2F1*	Gene/Protein
6	Retinoblastoma	*CDK6*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
7	Retinoblastoma	*RBBP4*	Gene/Protein
8	Retinoblastoma	*TCHP*	Gene/Protein
9	Retinoblastoma	*TSC1*	Gene/Protein
10	Retinoblastoma	*CCND1*	Gene/Protein
11	Retinoblastoma	*FHIT*	Gene/Protein
12	Retinoblastoma	*RBBP7*	Gene/Protein
13	Retinoblastoma	*TP53*	Gene/Protein
14	Retinoblastoma	*CTD*	Gene/Protein
15	Retinoblastoma	*RBBP6*	Gene/Protein
16	Retinoblastoma	*CDK2*	Gene/Protein
17	Retinoblastoma	*CDKN1A*	Gene/Protein
18	Retinoblastoma	*H3F3AP6*	Gene/Protein
19	Retinoblastoma	*TCEAL1*	Gene/Protein
20	Retinoblastoma	*CDKN2A*	Gene/Protein
21	Retinoblastoma	*PRDM2*	Gene/Protein
22	Retinoblastoma	*E2F3*	Gene/Protein
23	Retinoblastoma	*MYCN*	Gene/Protein
24	Retinoblastoma	*LINC00202-1*	Gene/Protein
25	Retinoblastoma	*CCNE1*	Gene/Protein
26	Retinoblastoma	*CDKN1B*	Gene/Protein
27	Retinoblastoma	*LIN37*	Gene/Protein
28	Retinoblastoma	*E2F2*	Gene/Protein
29	Retinoblastoma	*ZNF890P*	Gene/Protein
30	Retinoblastoma	*SNORD115-41*	Gene/Protein
31	Retinoblastoma	*SNORD115-44*	Gene/Protein
32	Retinoblastoma	*MIR6724-4*	Gene/Protein
33	Retinoblastoma	*MRPL28*	Gene/Protein
34	Retinoblastoma	*LINC00441*	Gene/Protein
35	Retinoblastoma	*LIN52*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
36	Retinoblastoma	*MDM2*	Gene/Protein
37	Retinoblastoma	*E2F5*	Gene/Protein
38	Retinoblastoma	*RBP2*	Gene/Protein
39	Retinoblastoma	*E2F4*	Gene/Protein
40	Retinoblastoma	*SUB1*	Gene/Protein
41	Retinoblastoma	*CRX*	Gene/Protein
42	Retinoblastoma	*ZNF681*	Gene/Protein
43	Retinoblastoma	*USP46-AS1*	Gene/Protein
44	Retinoblastoma	*MIR765*	Gene/Protein
45	Retinoblastoma	*LOC100288590*	Gene/Protein
46	Retinoblastoma	*PPP1R26P1*	Gene/Protein
47	Retinoblastoma	*LOC100421630*	Gene/Protein
48	Retinoblastoma	*LOC100421663*	Gene/Protein
49	Retinoblastoma	*RBBP9*	Gene/Protein
50	Retinoblastoma	*KDM5A*	Gene/Protein
51	Retinoblastoma	*RIMBP2*	Gene/Protein
52	Retinoblastoma	*CDK1*	Gene/Protein
53	Retinoblastoma	*CDKN3*	Gene/Protein
54	Retinoblastoma	*MYC*	Gene/Protein
55	Retinoblastoma	*SKP2*	Gene/Protein
56	Retinoblastoma	*CCNA2*	Gene/Protein
57	Retinoblastoma	*CIB1*	Gene/Protein
58	Retinoblastoma	*SLC12A9*	Gene/Protein
59	Retinoblastoma	*LINC01257*	Gene/Protein
60	Retinoblastoma	*N4BP2L2-IT2*	Gene/Protein
61	Retinoblastoma	*ZFPM2-AS1*	Gene/Protein
62	Retinoblastoma	*CCND3*	Gene/Protein
63	Retinoblastoma	*E2F8*	Gene/Protein
64	Retinoblastoma	*LIN9*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
65	Retinoblastoma	*PTPN14*	Gene/Protein
66	Retinoblastoma	*HELLS*	Gene/Protein
67	Retinoblastoma	*ARHGAP28*	Gene/Protein
68	Retinoblastoma	*BBS9*	Gene/Protein
69	Retinoblastoma	*BIRC5*	Gene/Protein
70	Retinoblastoma	*LMOD1*	Gene/Protein
71	Retinoblastoma	*EMC9*	Gene/Protein
72	Retinoblastoma	*MDM4*	Gene/Protein
73	Retinoblastoma	*RBBP5*	Gene/Protein
74	Retinoblastoma	*KCNIP3*	Gene/Protein
75	Retinoblastoma	*PCDHB5*	Gene/Protein
76	Retinoblastoma	*MIR7-3*	Gene/Protein
77	Retinoblastoma	*FEZF1*	Gene/Protein
78	Retinoblastoma	*ZFPM2*	Gene/Protein
79	Retinoblastoma	*BCL2*	Gene/Protein
80	Retinoblastoma	*HIST1H4H*	Gene/Protein
81	Retinoblastoma	*CDK2AP2*	Gene/Protein
82	Retinoblastoma	*IGHD5-5*	Gene/Protein
83	Retinoblastoma	*ZCCHC2*	Gene/Protein
84	Retinoblastoma	*TMEM121*	Gene/Protein
85	Retinoblastoma	*LRRC39*	Gene/Protein
86	Retinoblastoma	*CCNB1*	Gene/Protein
87	Retinoblastoma	*PAK3*	Gene/Protein
88	Retinoblastoma	*FOXM1*	Gene/Protein
89	Retinoblastoma	*UBR4*	Gene/Protein
90	Retinoblastoma	*AFAP1-AS1*	Gene/Protein
91	Retinoblastoma	*UHRF1*	Gene/Protein
92	Retinoblastoma	*CDC25A*	Gene/Protein
93	Retinoblastoma	*DMXL1*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
94	Retinoblastoma	*CLUL1*	Gene/Protein
95	Retinoblastoma	*LINC00858*	Gene/Protein
96	Retinoblastoma	*FEZF1-AS1*	Gene/Protein
97	Retinoblastoma	*CASP3*	Gene/Protein
98	Retinoblastoma	*EID1*	Gene/Protein
99	Retinoblastoma	*GRAP2*	Gene/Protein
100	Retinoblastoma	*ARHGAP24*	Gene/Protein
101	Retinoblastoma	*KIF14*	Gene/Protein
102	Retinoblastoma	*MRPL48*	Gene/Protein
103	Retinoblastoma	*NLRP8*	Gene/Protein
104	Retinoblastoma	*PTEN*	Gene/Protein
105	Retinoblastoma	*LINC-PINT*	Gene/Protein
106	Retinoblastoma	*MCM7*	Gene/Protein
107	Retinoblastoma	*USP22*	Gene/Protein
108	Retinoblastoma	*CCND2*	Gene/Protein
109	Retinoblastoma	*POLD1*	Gene/Protein
110	Retinoblastoma	*CDKN2B-AS1*	Gene/Protein
111	Retinoblastoma	*SND1-IT1*	Gene/Protein
112	Retinoblastoma	*LDAH*	Gene/Protein
113	Retinoblastoma	*ACAD11*	Gene/Protein
114	Retinoblastoma	*SH3BP5-AS1*	Gene/Protein
115	Retinoblastoma	*BANCR*	Gene/Protein
116	Retinoblastoma	*MT1JP*	Gene/Protein
117	Retinoblastoma	*FBXO5*	Gene/Protein
118	Retinoblastoma	*MYBL2*	Gene/Protein
119	Retinoblastoma	*CDC25C*	Gene/Protein
120	Retinoblastoma	*RGN*	Gene/Protein
121	Retinoblastoma	*FRK*	Gene/Protein
122	Retinoblastoma	*BCOR*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
123	Retinoblastoma	*PAX6*	Gene/Protein
124	Retinoblastoma	*MTOR*	Gene/Protein
125	Retinoblastoma	*PPP1R10*	Gene/Protein
126	Retinoblastoma	*CDK7*	Gene/Protein
127	Retinoblastoma	*KIAA1456*	Gene/Protein
128	Retinoblastoma	*FRMD8*	Gene/Protein
129	Retinoblastoma	*FAM98B*	Gene/Protein
130	Retinoblastoma	*MIR506*	Gene/Protein
131	Retinoblastoma	*LINC00488*	Gene/Protein
132	Retinoblastoma	*ADPGK-AS1*	Gene/Protein
133	Retinoblastoma	*KLF16*	Gene/Protein
134	Retinoblastoma	*EPHA10*	Gene/Protein
135	Retinoblastoma	*CBR3-AS1*	Gene/Protein
136	Retinoblastoma	*MEG3*	Gene/Protein
137	Retinoblastoma	*TNS1*	Gene/Protein
138	Retinoblastoma	*ARL11*	Gene/Protein
139	Retinoblastoma	*LINC00908*	Gene/Protein
140	Retinoblastoma	*RNF6*	Gene/Protein
141	Retinoblastoma	*TP73-AS1*	Gene/Protein
142	Retinoblastoma	*CCNE2*	Gene/Protein
143	Retinoblastoma	*E2F7*	Gene/Protein
144	Retinoblastoma	*POMP*	Gene/Protein
145	Retinoblastoma	*LEF1-AS1*	Gene/Protein
146	Retinoblastoma	*RBAK*	Gene/Protein
147	Retinoblastoma	*TCEA1P2*	Gene/Protein
148	Retinoblastoma	*LASP1*	Gene/Protein
149	Retinoblastoma	*HDAC1*	Gene/Protein
150	Retinoblastoma	*CADM3*	Gene/Protein
151	Retinoblastoma	*AFAP1*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
152	Retinoblastoma	*MYCL*	Gene/Protein
153	Retinoblastoma	*MIR98*	Gene/Protein
154	Retinoblastoma	*MMP17*	Gene/Protein
155	Retinoblastoma	*TSPAN31*	Gene/Protein
156	Retinoblastoma	*CDKL1*	Gene/Protein
157	Retinoblastoma	*GALNT8*	Gene/Protein
158	Retinoblastoma	*CRYL1*	Gene/Protein
159	Retinoblastoma	*KBTBD4*	Gene/Protein
160	Retinoblastoma	*CENPP*	Gene/Protein
161	Retinoblastoma	*CD34*	Gene/Protein
162	Retinoblastoma	*OTX2*	Gene/Protein
163	Retinoblastoma	*ZFPM1*	Gene/Protein
164	Retinoblastoma	*SCLC1*	Gene/Protein
165	Retinoblastoma	*RBBP8*	Gene/Protein
166	Retinoblastoma	*BCL2L1*	Gene/Protein
167	Retinoblastoma	*PLK1*	Gene/Protein
168	Retinoblastoma	*SYK*	Gene/Protein
169	Retinoblastoma	*GNL1*	Gene/Protein
170	Retinoblastoma	*FBXO15*	Gene/Protein
171	Retinoblastoma	*TMEM9*	Gene/Protein
172	Retinoblastoma	*ESRG*	Gene/Protein
173	Retinoblastoma	*ELDR*	Gene/Protein
174	Retinoblastoma	*MIR17HG*	Gene/Protein
175	Retinoblastoma	*MED4*	Gene/Protein
176	Retinoblastoma	*BUB1*	Gene/Protein
177	Retinoblastoma	*SOX2*	Gene/Protein
178	Retinoblastoma	*ZNF645*	Gene/Protein
179	Retinoblastoma	*RPL41*	Gene/Protein
180	Retinoblastoma	*CIT*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
181	Retinoblastoma	*NLRP11*	Gene/Protein
182	Retinoblastoma	*MUL1*	Gene/Protein
183	Retinoblastoma	*SNHG16*	Gene/Protein
184	Retinoblastoma	*PRB2*	Gene/Protein
185	Retinoblastoma	*CDH1*	Gene/Protein
186	Retinoblastoma	*ENO2*	Gene/Protein
187	Retinoblastoma	*HMGA2*	Gene/Protein
188	Retinoblastoma	*SUSD2*	Gene/Protein
189	Retinoblastoma	*MKI67*	Gene/Protein
190	Retinoblastoma	*CASP9*	Gene/Protein
191	Retinoblastoma	*AUP1*	Gene/Protein
192	Retinoblastoma	*PHF20L1*	Gene/Protein
193	Retinoblastoma	*WSB2*	Gene/Protein
194	Retinoblastoma	*OTOR*	Gene/Protein
195	Retinoblastoma	*FBXL17*	Gene/Protein
196	Retinoblastoma	*TSTD1*	Gene/Protein
197	Retinoblastoma	*LINC00205*	Gene/Protein
198	Retinoblastoma	*ADAM19*	Gene/Protein
199	Retinoblastoma	*TFF1*	Gene/Protein
200	Retinoblastoma	*EZH2*	Gene/Protein
201	Retinoblastoma	*BCAR1*	Gene/Protein
202	Retinoblastoma	*AURKA*	Gene/Protein
203	Retinoblastoma	*NTMT1*	Gene/Protein
204	Retinoblastoma	*POLR1E*	Gene/Protein
205	Retinoblastoma	*LINC00115*	Gene/Protein
206	Retinoblastoma	*RHBDL3*	Gene/Protein
207	Retinoblastoma	*SBK1*	Gene/Protein
208	Retinoblastoma	*MBD2*	Gene/Protein
209	Retinoblastoma	*SYP*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
210	Retinoblastoma	*HOXB2*	Gene/Protein
211	Retinoblastoma	*CDKN2B*	Gene/Protein
212	Retinoblastoma	*NSG1*	Gene/Protein
213	Retinoblastoma	*RNF14*	Gene/Protein
214	Retinoblastoma	*FBXO21*	Gene/Protein
215	Retinoblastoma	*MRPS18B*	Gene/Protein
216	Retinoblastoma	*SERTAD3*	Gene/Protein
217	Retinoblastoma	*KTN1-AS1*	Gene/Protein
218	Retinoblastoma	*ABCB5*	Gene/Protein
219	Retinoblastoma	*CHEK1*	Gene/Protein
220	Retinoblastoma	*STAT3*	Gene/Protein
221	Retinoblastoma	*RBM45*	Gene/Protein
222	Retinoblastoma	*PARK2*	Gene/Protein
223	Retinoblastoma	*GPRIN2*	Gene/Protein
224	Retinoblastoma	*PPIL3*	Gene/Protein
225	Retinoblastoma	*PROX1-AS1*	Gene/Protein
226	Retinoblastoma	*CUL2*	Gene/Protein
227	Retinoblastoma	*LINC00152*	Gene/Protein
228	Retinoblastoma	*NEK6*	Gene/Protein
229	Retinoblastoma	*STX17*	Gene/Protein
230	Retinoblastoma	*ATRX*	Gene/Protein
231	Retinoblastoma	*SNRPB2*	Gene/Protein
232	Retinoblastoma	*ZNRD1-AS1*	Gene/Protein
233	Retinoblastoma	*WEE1*	Gene/Protein
234	Retinoblastoma	*SOX4*	Gene/Protein
235	Retinoblastoma	*CTDSPL*	Gene/Protein
236	Retinoblastoma	*BMI1*	Gene/Protein
237	Retinoblastoma	*NEAT1*	Gene/Protein
238	Retinoblastoma	*CDCA2*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
239	Retinoblastoma	*IFNA4*	Gene/Protein
240	Retinoblastoma	*NUFIP1*	Gene/Protein
241	Retinoblastoma	*LIN54*	Gene/Protein
242	Retinoblastoma	*PDCD4*	Gene/Protein
243	Retinoblastoma	*MEN1*	Gene/Protein
244	Retinoblastoma	*SKP1*	Gene/Protein
245	Retinoblastoma	*NFE2L3*	Gene/Protein
246	Retinoblastoma	*MAB21L1*	Gene/Protein
247	Retinoblastoma	*CEP350*	Gene/Protein
248	Retinoblastoma	*FBXO9*	Gene/Protein
249	Retinoblastoma	*RABL6*	Gene/Protein
250	Retinoblastoma	*TTC39B*	Gene/Protein
251	Retinoblastoma	*KPNA7*	Gene/Protein
252	Retinoblastoma	*MCM6*	Gene/Protein
253	Retinoblastoma	*PRMT5*	Gene/Protein
254	Retinoblastoma	*PVRL3*	Gene/Protein
255	Retinoblastoma	*ACVR1C*	Gene/Protein
256	Retinoblastoma	*CTNNB1*	Gene/Protein
257	Retinoblastoma	*COLGALT1*	Gene/Protein
258	Retinoblastoma	*TINCR*	Gene/Protein
259	Retinoblastoma	*MIR106B*	Gene/Protein
260	Retinoblastoma	*MIR19B1*	Gene/Protein
261	Retinoblastoma	*MELK*	Gene/Protein
262	Retinoblastoma	*HSPA4L*	Gene/Protein
263	Retinoblastoma	*LMNA*	Gene/Protein
264	Retinoblastoma	*PCGF3*	Gene/Protein
265	Retinoblastoma	*DRAM2*	Gene/Protein
266	Retinoblastoma	*PPP1R3F*	Gene/Protein
267	Retinoblastoma	*CREBBP*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
268	Retinoblastoma	*PROM1*	Gene/Protein
269	Retinoblastoma	*CCNH*	Gene/Protein
270	Retinoblastoma	*MTDH*	Gene/Protein
271	Retinoblastoma	*INSM1*	Gene/Protein
272	Retinoblastoma	*HBP1*	Gene/Protein
273	Retinoblastoma	*HLX*	Gene/Protein
274	Retinoblastoma	*EIF1AY*	Gene/Protein
275	Retinoblastoma	*TP53AIP1*	Gene/Protein
276	Retinoblastoma	*VWA1*	Gene/Protein
277	Retinoblastoma	*ILF3-AS1*	Gene/Protein
278	Retinoblastoma	*SLCO4A1-AS1*	Gene/Protein
279	Retinoblastoma	*APC*	Gene/Protein
280	Retinoblastoma	*MIR186*	Gene/Protein
281	Retinoblastoma	*PTK2B*	Gene/Protein
282	Retinoblastoma	*ABCA4*	Gene/Protein
283	Retinoblastoma	*AP1M2*	Gene/Protein
284	Retinoblastoma	*RDM1*	Gene/Protein
285	Retinoblastoma	*CRABP1*	Gene/Protein
286	Retinoblastoma	*CCNA1*	Gene/Protein
287	Retinoblastoma	*PPP1R9B*	Gene/Protein
288	Retinoblastoma	*CDC6*	Gene/Protein
289	Retinoblastoma	*DNMT1*	Gene/Protein
290	Retinoblastoma	*NOTCH1*	Gene/Protein
291	Retinoblastoma	*PRDM16*	Gene/Protein
292	Retinoblastoma	*HIF1A*	Gene/Protein
293	Retinoblastoma	*TFDP1*	Gene/Protein
294	Retinoblastoma	*FZR1*	Gene/Protein
295	Retinoblastoma	*DTX4*	Gene/Protein
296	Retinoblastoma	*SMARCE1*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
297	Retinoblastoma	*FOXD2-AS1*	Gene/Protein
298	Retinoblastoma	*CDC25B*	Gene/Protein
299	Retinoblastoma	*DMAP1*	Gene/Protein
300	Retinoblastoma	*KCNQ1OT1*	Gene/Protein
301	Retinoblastoma	*ARID4A*	Gene/Protein
302	Retinoblastoma	*NKILA*	Gene/Protein
303	Retinoblastoma	*IER2*	Gene/Protein
304	Retinoblastoma	*FBXO28*	Gene/Protein
305	Retinoblastoma	*TCL6*	Gene/Protein
306	Retinoblastoma	*LUZP4*	Gene/Protein
307	Retinoblastoma	*IER5*	Gene/Protein
308	Retinoblastoma	*TRPM2-AS*	Gene/Protein
309	Retinoblastoma	*MMP2*	Gene/Protein
310	Retinoblastoma	*PLK3*	Gene/Protein
311	Retinoblastoma	*HMGA1*	Gene/Protein
312	Retinoblastoma	*DICER1*	Gene/Protein
313	Retinoblastoma	*ZACN*	Gene/Protein
314	Retinoblastoma	*PLAC8*	Gene/Protein
315	Retinoblastoma	*UBE2H*	Gene/Protein
316	Retinoblastoma	*DAZAP1*	Gene/Protein
317	Retinoblastoma	*VEGFA*	Gene/Protein
318	Retinoblastoma	*HIST1H1C*	Gene/Protein
319	Retinoblastoma	*GPR143*	Gene/Protein
320	Retinoblastoma	*MAPK12*	Gene/Protein
321	Retinoblastoma	*BLM*	Gene/Protein
322	Retinoblastoma	*PPP1CA*	Gene/Protein
323	Retinoblastoma	*MMP9*	Gene/Protein
324	Retinoblastoma	*RRM2*	Gene/Protein
325	Retinoblastoma	*SUPT3H*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
326	Retinoblastoma	*TWSG1*	Gene/Protein
327	Retinoblastoma	*HELZ2*	Gene/Protein
328	Retinoblastoma	*ANKLE1*	Gene/Protein
329	Retinoblastoma	*PA2G4*	Gene/Protein
330	Retinoblastoma	*EGFR*	Gene/Protein
331	Retinoblastoma	*RPS6KA4*	Gene/Protein
332	Retinoblastoma	*ZBTB33*	Gene/Protein
333	Retinoblastoma	*MYCNOS*	Gene/Protein
334	Retinoblastoma	*ENOX1*	Gene/Protein
335	Retinoblastoma	*CAMKK1*	Gene/Protein
336	Retinoblastoma	*DCAF15*	Gene/Protein
337	Retinoblastoma	*NDUFAF2*	Gene/Protein
338	Retinoblastoma	*GPR151*	Gene/Protein
339	Retinoblastoma	*DRAIC*	Gene/Protein
340	Retinoblastoma	*NANOGP8*	Gene/Protein
341	Retinoblastoma	*SNHG14*	Gene/Protein
342	Retinoblastoma	*NANOG*	Gene/Protein
343	Retinoblastoma	*PARP1*	Gene/Protein
344	Retinoblastoma	*PCNA*	Gene/Protein
345	Retinoblastoma	*CDH18*	Gene/Protein
346	Retinoblastoma	*HBZ*	Gene/Protein
347	Retinoblastoma	*PPP5C*	Gene/Protein
348	Retinoblastoma	*UBE2E1*	Gene/Protein
349	Retinoblastoma	*ZMYM3*	Gene/Protein
350	Retinoblastoma	*EHBP1*	Gene/Protein
351	Retinoblastoma	*CTAGE1*	Gene/Protein
352	Retinoblastoma	*PCGF1*	Gene/Protein
353	Retinoblastoma	*UNC5D*	Gene/Protein
354	Retinoblastoma	*HOXB5*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
355	Retinoblastoma	*SMARCA4*	Gene/Protein
356	Retinoblastoma	*CCNI*	Gene/Protein
357	Retinoblastoma	*CDC73*	Gene/Protein
358	Retinoblastoma	*DES*	Gene/Protein
359	Retinoblastoma	*HDAC9*	Gene/Protein
360	Retinoblastoma	*KAT2B*	Gene/Protein
361	Retinoblastoma	*CDKN1C*	Gene/Protein
362	Retinoblastoma	*LRP6*	Gene/Protein
363	Retinoblastoma	*CDC14B*	Gene/Protein
364	Retinoblastoma	*CCPG1*	Gene/Protein
365	Retinoblastoma	*PTPN21*	Gene/Protein
366	Retinoblastoma	*SUCLA2*	Gene/Protein
367	Retinoblastoma	*RIN1*	Gene/Protein
368	Retinoblastoma	*ADGRA3*	Gene/Protein
369	Retinoblastoma	*BCL2L15*	Gene/Protein
370	Retinoblastoma	*DNM3OS*	Gene/Protein
371	Retinoblastoma	*EP300*	Gene/Protein
372	Retinoblastoma	*UCA1*	Gene/Protein
373	Retinoblastoma	*RPL23A*	Gene/Protein
374	Retinoblastoma	*RPL30*	Gene/Protein
375	Retinoblastoma	*CCNF*	Gene/Protein
376	Retinoblastoma	*PIK3CA*	Gene/Protein
377	Retinoblastoma	*COL11A2*	Gene/Protein
378	Retinoblastoma	*CDK18*	Gene/Protein
379	Retinoblastoma	*TCF19*	Gene/Protein
380	Retinoblastoma	*ARID3B*	Gene/Protein
381	Retinoblastoma	*RNF123*	Gene/Protein
382	Retinoblastoma	*MYCT1*	Gene/Protein
383	Retinoblastoma	*CKS1B*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
384	Retinoblastoma	*ATAD2*	Gene/Protein
385	Retinoblastoma	*UBASH3B*	Gene/Protein
386	Retinoblastoma	*NARFL*	Gene/Protein
387	Retinoblastoma	*RHPN1-AS1*	Gene/Protein
388	Retinoblastoma	*PRUNE2*	Gene/Protein
389	Retinoblastoma	*POU5F1*	Gene/Protein
390	Retinoblastoma	*JUN*	Gene/Protein
391	Retinoblastoma	*NF1*	Gene/Protein
392	Retinoblastoma	*INPP4B*	Gene/Protein
393	Retinoblastoma	*EXOSC8*	Gene/Protein
394	Retinoblastoma	*NRCAM*	Gene/Protein
395	Retinoblastoma	*MIR7-3HG*	Gene/Protein
396	Retinoblastoma	*CROCC*	Gene/Protein
397	Retinoblastoma	*INGX*	Gene/Protein
398	Retinoblastoma	*ETAA1*	Gene/Protein
399	Retinoblastoma	*ADGRL4*	Gene/Protein
400	Retinoblastoma	*ERBB2*	Gene/Protein
401	Retinoblastoma	*EIF4EBP1*	Gene/Protein
402	Retinoblastoma	*GDF1*	Gene/Protein
403	Retinoblastoma	*MKLN1*	Gene/Protein
404	Retinoblastoma	*RXRB*	Gene/Protein
405	Retinoblastoma	*KPNA6*	Gene/Protein
406	Retinoblastoma	*C14orf166*	Gene/Protein
407	Retinoblastoma	*IL17RE*	Gene/Protein
408	Retinoblastoma	*RASSF6*	Gene/Protein
409	Retinoblastoma	*CDK5*	Gene/Protein
410	Retinoblastoma	*MIR192*	Gene/Protein
411	Retinoblastoma	*PIN1*	Gene/Protein
412	Retinoblastoma	*ZEB1*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
413	Retinoblastoma	*ELFN1-AS1*	Gene/Protein
414	Retinoblastoma	*MIR34A*	Gene/Protein
415	Retinoblastoma	*ANXA6*	Gene/Protein
416	Retinoblastoma	*XIAP*	Gene/Protein
417	Retinoblastoma	*ABCB1*	Gene/Protein
418	Retinoblastoma	*RBP3*	Gene/Protein
419	Retinoblastoma	*REEP5*	Gene/Protein
420	Retinoblastoma	*VIM*	Gene/Protein
421	Retinoblastoma	*CASC8*	Gene/Protein
422	Retinoblastoma	*RBFOX2*	Gene/Protein
423	Retinoblastoma	*PDZD2*	Gene/Protein
424	Retinoblastoma	*MIR17*	Gene/Protein
425	Retinoblastoma	*FAT4*	Gene/Protein
426	Retinoblastoma	*NUP205*	Gene/Protein
427	Retinoblastoma	*WSB1*	Gene/Protein
428	Retinoblastoma	*CHUK*	Gene/Protein
429	Retinoblastoma	*ESRRG*	Gene/Protein
430	Retinoblastoma	*WNT2B*	Gene/Protein
431	Retinoblastoma	*AKAP12*	Gene/Protein
432	Retinoblastoma	*H2AFX*	Gene/Protein
433	Retinoblastoma	*LIN28A*	Gene/Protein
434	Retinoblastoma	*MIR31*	Gene/Protein
435	Retinoblastoma	*ZNF77*	Gene/Protein
436	Retinoblastoma	*MVP*	Gene/Protein
437	Retinoblastoma	*SOX30*	Gene/Protein
438	Retinoblastoma	*USP33*	Gene/Protein
439	Retinoblastoma	*LILRA6*	Gene/Protein
440	Retinoblastoma	*TMPO*	Gene/Protein
441	Retinoblastoma	*ERRFI1*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
442	Retinoblastoma	*AKAP8*	Gene/Protein
443	Retinoblastoma	*WWTR1*	Gene/Protein
444	Retinoblastoma	*CDK2AP1*	Gene/Protein
445	Retinoblastoma	*NR4A1*	Gene/Protein
446	Retinoblastoma	*ABCB7*	Gene/Protein
447	Retinoblastoma	*LIMD1*	Gene/Protein
448	Retinoblastoma	*GNL2*	Gene/Protein
449	Retinoblastoma	*ZNF83*	Gene/Protein
450	Retinoblastoma	*ZBTB4*	Gene/Protein
451	Retinoblastoma	*ZNF367*	Gene/Protein
452	Retinoblastoma	*LINC00324*	Gene/Protein
453	Retinoblastoma	*TRIP11*	Gene/Protein
454	Retinoblastoma	*TP53TG1*	Gene/Protein
455	Retinoblastoma	*CCNDBP1*	Gene/Protein
456	Retinoblastoma	*RHOV*	Gene/Protein
457	Retinoblastoma	*NEK7*	Gene/Protein
458	Retinoblastoma	*TERT*	Gene/Protein
459	Retinoblastoma	*BCL2L11*	Gene/Protein
460	Retinoblastoma	*CDK3*	Gene/Protein
461	Retinoblastoma	*PSMA5*	Gene/Protein
462	Retinoblastoma	*CDK10*	Gene/Protein
463	Retinoblastoma	*CDC23*	Gene/Protein
464	Retinoblastoma	*RABAC1*	Gene/Protein
465	Retinoblastoma	*AMBRA1*	Gene/Protein
466	Retinoblastoma	*MET*	Gene/Protein
467	Retinoblastoma	*UBE2T*	Gene/Protein
468	Retinoblastoma	*ERI1*	Gene/Protein
469	Retinoblastoma	*RCVRN*	Gene/Protein
470	Retinoblastoma	*CORO1A*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
471	Retinoblastoma	*PKLR*	Gene/Protein
472	Retinoblastoma	*HSPB1*	Gene/Protein
473	Retinoblastoma	*EIF1AX*	Gene/Protein
474	Retinoblastoma	*DACT2*	Gene/Protein
475	Retinoblastoma	*HEIH*	Gene/Protein
476	Retinoblastoma	*MALAT1*	Gene/Protein
477	Retinoblastoma	*LGALS13*	Gene/Protein
478	Retinoblastoma	*THRB*	Gene/Protein
479	Retinoblastoma	*GTF3C1*	Gene/Protein
480	Retinoblastoma	*CCNK*	Gene/Protein
481	Retinoblastoma	*TENM1*	Gene/Protein
482	Retinoblastoma	*USP29*	Gene/Protein
483	Retinoblastoma	*VHL*	Gene/Protein
484	Retinoblastoma	*YWHAG*	Gene/Protein
485	Retinoblastoma	*CCAT1*	Gene/Protein
486	Retinoblastoma	*MAP1LC3B*	Gene/Protein
487	Retinoblastoma	*DAXX*	Gene/Protein
488	Retinoblastoma	*SUZ12*	Gene/Protein
489	Retinoblastoma	*SRSF3*	Gene/Protein
490	Retinoblastoma	*MECOM*	Gene/Protein
491	Retinoblastoma	*PEG10*	Gene/Protein
492	Retinoblastoma	*MATN2*	Gene/Protein
493	Retinoblastoma	*DEAF1*	Gene/Protein
494	Retinoblastoma	*AGFG2*	Gene/Protein
495	Retinoblastoma	*CDK9*	Gene/Protein
496	Retinoblastoma	*HRAS*	Gene/Protein
497	Retinoblastoma	*KRAS*	Gene/Protein
498	Retinoblastoma	*CRB1*	Gene/Protein
499	Retinoblastoma	*LMNB1*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
500	Retinoblastoma	*ASCL1*	Gene/Protein
501	Retinoblastoma	*ROM1*	Gene/Protein
502	Retinoblastoma	*CDK5R1*	Gene/Protein
503	Retinoblastoma	*MCM2*	Gene/Protein
504	Retinoblastoma	*LIN28B*	Gene/Protein
505	Retinoblastoma	*MCM4*	Gene/Protein
506	Retinoblastoma	*RASSF2*	Gene/Protein
507	Retinoblastoma	*ADGRG2*	Gene/Protein
508	Retinoblastoma	*ELL2*	Gene/Protein
509	Retinoblastoma	*HPS1*	Gene/Protein
510	Retinoblastoma	*MAP3K10*	Gene/Protein
511	Retinoblastoma	*DYNLT1*	Gene/Protein
512	Retinoblastoma	*FER1L4*	Gene/Protein
513	Retinoblastoma	*FOXR2*	Gene/Protein
514	Retinoblastoma	*ZBTB46*	Gene/Protein
515	Retinoblastoma	*SMAD2*	Gene/Protein
516	Retinoblastoma	*PSMD10*	Gene/Protein
517	Retinoblastoma	*RCC1*	Gene/Protein
518	Retinoblastoma	*KIAA1524*	Gene/Protein
519	Retinoblastoma	*RAP2B*	Gene/Protein
520	Retinoblastoma	*RRN3*	Gene/Protein
521	Retinoblastoma	*DANCR*	Gene/Protein
522	Retinoblastoma	*NOTCH2*	Gene/Protein
523	Retinoblastoma	*TOPBP1*	Gene/Protein
524	Retinoblastoma	*AURKB*	Gene/Protein
525	Retinoblastoma	*RGPD2*	Gene/Protein
526	Retinoblastoma	*PML*	Gene/Protein
527	Retinoblastoma	*EPCAM*	Gene/Protein
528	Retinoblastoma	*HNF4G*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
529	Retinoblastoma	*KIR2DS5*	Gene/Protein
530	Retinoblastoma	*PIK3C2B*	Gene/Protein
531	Retinoblastoma	*LEFTY2*	Gene/Protein
532	Retinoblastoma	*UBE2G2*	Gene/Protein
533	Retinoblastoma	*BAZ1A*	Gene/Protein
534	Retinoblastoma	*NEDD8*	Gene/Protein
535	Retinoblastoma	*LRIG2*	Gene/Protein
536	Retinoblastoma	*LOXL1-AS1*	Gene/Protein
537	Retinoblastoma	*ARRDC3*	Gene/Protein
538	Retinoblastoma	*PIK3R1*	Gene/Protein
539	Retinoblastoma	*WNK1*	Gene/Protein
540	Retinoblastoma	*FAT2*	Gene/Protein
541	Retinoblastoma	*SRSF7*	Gene/Protein
542	Retinoblastoma	*CDK5R2*	Gene/Protein
543	Retinoblastoma	*PKP3*	Gene/Protein
544	Retinoblastoma	*ARHGEF15*	Gene/Protein
545	Retinoblastoma	*NCAPH*	Gene/Protein
546	Retinoblastoma	*TENM3*	Gene/Protein
547	Retinoblastoma	*ANAPC1*	Gene/Protein
548	Retinoblastoma	*SNHG20*	Gene/Protein
549	Retinoblastoma	*TMPO-AS1*	Gene/Protein
550	Retinoblastoma	*HUWE1*	Gene/Protein
551	Retinoblastoma	*PHF6*	Gene/Protein
552	Retinoblastoma	*ARIH1*	Gene/Protein
553	Retinoblastoma	*NBEA*	Gene/Protein
554	Retinoblastoma	*PCDH17*	Gene/Protein
555	Retinoblastoma	*RP1L1*	Gene/Protein
556	Retinoblastoma	*APAF1*	Gene/Protein
557	Retinoblastoma	*TFF3*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
558	Retinoblastoma	*EFNB3*	Gene/Protein
559	Retinoblastoma	*CDKN2D*	Gene/Protein
560	Retinoblastoma	*PROX1*	Gene/Protein
561	Retinoblastoma	*HOXC9*	Gene/Protein
562	Retinoblastoma	*KTN1*	Gene/Protein
563	Retinoblastoma	*PRB1*	Gene/Protein
564	Retinoblastoma	*UVRAG*	Gene/Protein
565	Retinoblastoma	*SLC37A1*	Gene/Protein
566	Retinoblastoma	*SPTLC3*	Gene/Protein
567	Retinoblastoma	*HES6*	Gene/Protein
568	Retinoblastoma	*USP48*	Gene/Protein
569	Retinoblastoma	*MIR184*	Gene/Protein
570	Retinoblastoma	*MTHFR*	Gene/Protein
571	Retinoblastoma	*KDM6A*	Gene/Protein
572	Retinoblastoma	*NXT1*	Gene/Protein
573	Retinoblastoma	*CBR3*	Gene/Protein
574	Retinoblastoma	*SLC24A2*	Gene/Protein
575	Retinoblastoma	*DPY30*	Gene/Protein
576	Retinoblastoma	*DIRC2*	Gene/Protein
577	Retinoblastoma	*PTGDR*	Gene/Protein
578	Retinoblastoma	*QRSL1*	Gene/Protein
579	Retinoblastoma	*MIR145*	Gene/Protein
580	Retinoblastoma	*AKAP1*	Gene/Protein
581	Retinoblastoma	*IRS4*	Gene/Protein
582	Retinoblastoma	*TENM4*	Gene/Protein
583	Retinoblastoma	*AHNAK2*	Gene/Protein
584	Retinoblastoma	*KDM1B*	Gene/Protein
585	Retinoblastoma	*SP1*	Gene/Protein
586	Retinoblastoma	*CHEK2*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
587	Retinoblastoma	*ZNF135*	Gene/Protein
588	Retinoblastoma	*AKT1*	Gene/Protein
589	Retinoblastoma	*OPN1MW*	Gene/Protein
590	Retinoblastoma	*STAG3*	Gene/Protein
591	Retinoblastoma	*EXOC4*	Gene/Protein
592	Retinoblastoma	*HES5*	Gene/Protein
593	Retinoblastoma	*CRBN*	Gene/Protein
594	Retinoblastoma	*UPK2*	Gene/Protein
595	Retinoblastoma	*TARS2*	Gene/Protein
596	Retinoblastoma	*SKA3*	Gene/Protein
597	Retinoblastoma	*FSTL1*	Gene/Protein
598	Retinoblastoma	*ELK4*	Gene/Protein
599	Retinoblastoma	*FANCF*	Gene/Protein
600	Retinoblastoma	*IGKV3-15*	Gene/Protein
601	Retinoblastoma	*WHSC1*	Gene/Protein
602	Retinoblastoma	*H3F3A*	Gene/Protein
603	Retinoblastoma	*MIR137*	Gene/Protein
604	Retinoblastoma	*ILF3*	Gene/Protein
605	Retinoblastoma	*RPL19*	Gene/Protein
606	Retinoblastoma	*LILRB3*	Gene/Protein
607	Retinoblastoma	*IQGAP3*	Gene/Protein
608	Retinoblastoma	*KIF20A*	Gene/Protein
609	Retinoblastoma	*ECM1*	Gene/Protein
610	Retinoblastoma	*ABCG2*	Gene/Protein
611	Retinoblastoma	*RPS20*	Gene/Protein
612	Retinoblastoma	*UBE2E2*	Gene/Protein
613	Retinoblastoma	*MLYCD*	Gene/Protein
614	Retinoblastoma	*DNMT3B*	Gene/Protein
615	Retinoblastoma	*MACC1*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
616	Retinoblastoma	*IL11RA*	Gene/Protein
617	Retinoblastoma	*PFKFB2*	Gene/Protein
618	Retinoblastoma	*WNT8A*	Gene/Protein
619	Retinoblastoma	*NSDHL*	Gene/Protein
620	Retinoblastoma	*BRAF*	Gene/Protein
621	Retinoblastoma	*RAB31*	Gene/Protein
622	Retinoblastoma	*MKL2*	Gene/Protein
623	Retinoblastoma	*ARHGAP18*	Gene/Protein
624	Retinoblastoma	*BATF2*	Gene/Protein
625	Retinoblastoma	*CALD1*	Gene/Protein
626	Retinoblastoma	*BUB1B*	Gene/Protein
627	Retinoblastoma	*DHFR*	Gene/Protein
628	Retinoblastoma	*ROCK1*	Gene/Protein
629	Retinoblastoma	*PDE6C*	Gene/Protein
630	Retinoblastoma	*CDCA7*	Gene/Protein
631	Retinoblastoma	*CANT1*	Gene/Protein
632	Retinoblastoma	*SENP1*	Gene/Protein
633	Retinoblastoma	*TUG1*	Gene/Protein
634	Retinoblastoma	*RTCB*	Gene/Protein
635	Retinoblastoma	*GTSE1*	Gene/Protein
636	Retinoblastoma	*PDK1*	Gene/Protein
637	Retinoblastoma	*GNAQ*	Gene/Protein
638	Retinoblastoma	*CASP8*	Gene/Protein
639	Retinoblastoma	*OPN1LW*	Gene/Protein
640	Retinoblastoma	*RRS1*	Gene/Protein
641	Retinoblastoma	*STK26*	Gene/Protein
642	Retinoblastoma	*ASXL2*	Gene/Protein
643	Retinoblastoma	*FAT3*	Gene/Protein
644	Retinoblastoma	*DYRK1A*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
645	Retinoblastoma	*CENPE*	Gene/Protein
646	Retinoblastoma	*PNKP*	Gene/Protein
647	Retinoblastoma	*MTF2*	Gene/Protein
648	Retinoblastoma	*CASC9*	Gene/Protein
649	Retinoblastoma	*KDM6B*	Gene/Protein
650	Retinoblastoma	*RAF1*	Gene/Protein
651	Retinoblastoma	*WNK2*	Gene/Protein
652	Retinoblastoma	*LY9*	Gene/Protein
653	Retinoblastoma	*MED23*	Gene/Protein
654	Retinoblastoma	*TLK1*	Gene/Protein
655	Retinoblastoma	*RASSF5*	Gene/Protein
656	Retinoblastoma	*TMEM26*	Gene/Protein
657	Retinoblastoma	*HMGB1*	Gene/Protein
658	Retinoblastoma	*CELSR3*	Gene/Protein
659	Retinoblastoma	*PRELP*	Gene/Protein
660	Retinoblastoma	*KLF8*	Gene/Protein
661	Retinoblastoma	*RAB3GAP1*	Gene/Protein
662	Retinoblastoma	*HIST1H2AH*	Gene/Protein
663	Retinoblastoma	*MIR20A*	Gene/Protein
664	Retinoblastoma	*CDH2*	Gene/Protein
665	Retinoblastoma	*DDB1*	Gene/Protein
666	Retinoblastoma	*ATP6V0D1*	Gene/Protein
667	Retinoblastoma	*CDCA3*	Gene/Protein
668	Retinoblastoma	*CSMD3*	Gene/Protein
669	Retinoblastoma	*SLC9A1*	Gene/Protein
670	Retinoblastoma	*TRADD*	Gene/Protein
671	Retinoblastoma	*KLF2*	Gene/Protein
672	Retinoblastoma	*TCEA1*	Gene/Protein
673	Retinoblastoma	*TNR*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
674	Retinoblastoma	*NOLC1*	Gene/Protein
675	Retinoblastoma	*MIR198*	Gene/Protein
676	Retinoblastoma	*L1CAM*	Gene/Protein
677	Retinoblastoma	*PRC1*	Gene/Protein
678	Retinoblastoma	*GDF10*	Gene/Protein
679	Retinoblastoma	*LMO7*	Gene/Protein
680	Retinoblastoma	*NUP107*	Gene/Protein
681	Retinoblastoma	*MCL1*	Gene/Protein
682	Retinoblastoma	*CDH11*	Gene/Protein
683	Retinoblastoma	*WNT9A*	Gene/Protein
684	Retinoblastoma	*AMER1*	Gene/Protein
685	Retinoblastoma	*C1D*	Gene/Protein
686	Retinoblastoma	*NRAS*	Gene/Protein
687	Retinoblastoma	*FGFR4*	Gene/Protein
688	Retinoblastoma	*PDPK1*	Gene/Protein
689	Retinoblastoma	*AR*	Gene/Protein
690	Retinoblastoma	*LRG1*	Gene/Protein
691	Retinoblastoma	*ING3*	Gene/Protein
692	Retinoblastoma	*TARSL2*	Gene/Protein
693	Retinoblastoma	*PSG1*	Gene/Protein
694	Retinoblastoma	*MYOG*	Gene/Protein
695	Retinoblastoma	*SMAD4*	Gene/Protein
696	Retinoblastoma	*PHOX2B*	Gene/Protein
697	Retinoblastoma	*MT1G*	Gene/Protein
698	Retinoblastoma	*MUTYH*	Gene/Protein
699	Retinoblastoma	*SMC2*	Gene/Protein
700	Retinoblastoma	*CPT1B*	Gene/Protein
701	Retinoblastoma	*NODAL*	Gene/Protein
702	Retinoblastoma	*HSF1*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
703	Retinoblastoma	*DDX1*	Gene/Protein
704	Retinoblastoma	*TUSC3*	Gene/Protein
705	Retinoblastoma	*TIGAR*	Gene/Protein
706	Retinoblastoma	*CCNB3*	Gene/Protein
707	Retinoblastoma	*SCARA5*	Gene/Protein
708	Retinoblastoma	*PRKCD*	Gene/Protein
709	Retinoblastoma	*SLC2A1*	Gene/Protein
710	Retinoblastoma	*ODC1*	Gene/Protein
711	Retinoblastoma	*DAND5*	Gene/Protein
712	Retinoblastoma	*UBE2M*	Gene/Protein
713	Retinoblastoma	*NUDT21*	Gene/Protein
714	Retinoblastoma	*BCORL1*	Gene/Protein
715	Retinoblastoma	*DIXDC1*	Gene/Protein
716	Retinoblastoma	*CXCR4*	Gene/Protein
717	Retinoblastoma	*RPL36A*	Gene/Protein
718	Retinoblastoma	*PPP1R3E*	Gene/Protein
719	Retinoblastoma	*PPP1R37*	Gene/Protein
720	Retinoblastoma	*DDR2*	Gene/Protein
721	Retinoblastoma	*EPHB6*	Gene/Protein
722	Retinoblastoma	*SYNJ2BP*	Gene/Protein
723	Retinoblastoma	*CSRNP2*	Gene/Protein
724	Retinoblastoma	*ZCCHC9*	Gene/Protein
725	Retinoblastoma	*RDH12*	Gene/Protein
726	Retinoblastoma	*PPP1R36*	Gene/Protein
727	Retinoblastoma	*TRIM42*	Gene/Protein
728	Retinoblastoma	*WNT3A*	Gene/Protein
729	Retinoblastoma	*SH3GL2*	Gene/Protein
730	Retinoblastoma	*PPP1R26*	Gene/Protein
731	Retinoblastoma	*PPP1R27*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
732	Retinoblastoma	*ZSWIM3*	Gene/Protein
733	Retinoblastoma	*NPY4R*	Gene/Protein
734	Retinoblastoma	*GSTA4*	Gene/Protein
735	Retinoblastoma	*NPFF*	Gene/Protein
736	Retinoblastoma	*CUL7*	Gene/Protein
737	Retinoblastoma	*FKBP15*	Gene/Protein
738	Retinoblastoma	*PPP1R14D*	Gene/Protein
739	Retinoblastoma	*PPP1R32*	Gene/Protein
740	Retinoblastoma	*PPP1R35*	Gene/Protein
741	Retinoblastoma	*PPP1R42*	Gene/Protein
742	Retinoblastoma	*TMEM225*	Gene/Protein
743	Retinoblastoma	*RMRP*	Gene/Protein
744	Retinoblastoma	*UBE2C*	Gene/Protein
745	Retinoblastoma	*MRPL23*	Gene/Protein
746	Retinoblastoma	*SLC16A8*	Gene/Protein
747	Retinoblastoma	*PPP1R16A*	Gene/Protein
748	Retinoblastoma	*SPON1*	Gene/Protein
749	Retinoblastoma	*ZWINT*	Gene/Protein
750	Retinoblastoma	*DUSP10*	Gene/Protein
751	Retinoblastoma	*GPATCH2*	Gene/Protein
752	Retinoblastoma	*OSCP1*	Gene/Protein
753	Retinoblastoma	*JAG2*	Gene/Protein
754	Retinoblastoma	*NME1*	Gene/Protein
755	Retinoblastoma	*NR2F1*	Gene/Protein
756	Retinoblastoma	*AXL*	Gene/Protein
757	Retinoblastoma	*CCNG2*	Gene/Protein
758	Retinoblastoma	*CLDN8*	Gene/Protein
759	Retinoblastoma	*TRIM44*	Gene/Protein
760	Retinoblastoma	*DDX31*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
761	Retinoblastoma	*HOTAIR*	Gene/Protein
762	Retinoblastoma	*CKS2*	Gene/Protein
763	Retinoblastoma	*WIF1*	Gene/Protein
764	Retinoblastoma	*PPP1R3D*	Gene/Protein
765	Retinoblastoma	*TARS*	Gene/Protein
766	Retinoblastoma	*TSKS*	Gene/Protein
767	Retinoblastoma	*AGO4*	Gene/Protein
768	Retinoblastoma	*PHF8*	Gene/Protein
769	Retinoblastoma	*YLPM1*	Gene/Protein
770	Retinoblastoma	*CSRNP3*	Gene/Protein
771	Retinoblastoma	*PPP1R21*	Gene/Protein
772	Retinoblastoma	*TRIM71*	Gene/Protein
773	Retinoblastoma	*PPP1R1C*	Gene/Protein
774	Retinoblastoma	*MIR32*	Gene/Protein
775	Retinoblastoma	*TXK*	Gene/Protein
776	Retinoblastoma	*PPP1R17*	Gene/Protein
777	Retinoblastoma	*ADGRL3*	Gene/Protein
778	Retinoblastoma	*PPP1R14C*	Gene/Protein
779	Retinoblastoma	*ELFN2*	Gene/Protein
780	Retinoblastoma	*SUMO1*	Gene/Protein
781	Retinoblastoma	*RPS6KA1*	Gene/Protein
782	Retinoblastoma	*NDC80*	Gene/Protein
783	Retinoblastoma	*SUV39H1*	Gene/Protein
784	Retinoblastoma	*ACTL6A*	Gene/Protein
785	Retinoblastoma	*DZIP3*	Gene/Protein
786	Retinoblastoma	*ANKRD28*	Gene/Protein
787	Retinoblastoma	*TRPC4AP*	Gene/Protein
788	Retinoblastoma	*PHACTR4*	Gene/Protein
789	Retinoblastoma	*SLC5A5*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
790	Retinoblastoma	*CYR61*	Gene/Protein
791	Retinoblastoma	*MEIS1*	Gene/Protein
792	Retinoblastoma	*CD2BP2*	Gene/Protein
793	Retinoblastoma	*SRPX2*	Gene/Protein
794	Retinoblastoma	*SH2D4A*	Gene/Protein
795	Retinoblastoma	*LMF1*	Gene/Protein
796	Retinoblastoma	*TMEM132C*	Gene/Protein
797	Retinoblastoma	*MIRLET7B*	Gene/Protein
798	Retinoblastoma	*MIR183*	Gene/Protein
799	Retinoblastoma	*PDE8B*	Gene/Protein
800	Retinoblastoma	*PPP1R14B*	Gene/Protein
801	Retinoblastoma	*WBP11*	Gene/Protein
802	Retinoblastoma	*SH3RF2*	Gene/Protein
803	Retinoblastoma	*EYS*	Gene/Protein
804	Retinoblastoma	*RPS6P1*	Gene/Protein
805	Retinoblastoma	*BECN1*	Gene/Protein
806	Retinoblastoma	*PTTG1*	Gene/Protein
807	Retinoblastoma	*IKBKG*	Gene/Protein
808	Retinoblastoma	*PTPN12*	Gene/Protein
809	Retinoblastoma	*PPFIBP1*	Gene/Protein
810	Retinoblastoma	*GMNN*	Gene/Protein
811	Retinoblastoma	*CHCHD6*	Gene/Protein
812	Retinoblastoma	*GRXCR1*	Gene/Protein
813	Retinoblastoma	*FER*	Gene/Protein
814	Retinoblastoma	*BCL2L2*	Gene/Protein
815	Retinoblastoma	*PARP2*	Gene/Protein
816	Retinoblastoma	*GDF3*	Gene/Protein
817	Retinoblastoma	*SAE1*	Gene/Protein
818	Retinoblastoma	*PHACTR3*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
819	Retinoblastoma	*PPP1R3G*	Gene/Protein
820	Retinoblastoma	*PRKD1*	Gene/Protein
821	Retinoblastoma	*PPP1R7*	Gene/Protein
822	Retinoblastoma	*KIAA0430*	Gene/Protein
823	Retinoblastoma	*ALYREF*	Gene/Protein
824	Retinoblastoma	*NOM1*	Gene/Protein
825	Retinoblastoma	*PPP1R18*	Gene/Protein
826	Retinoblastoma	*SLC10A5*	Gene/Protein
827	Retinoblastoma	*DUSP6*	Gene/Protein
828	Retinoblastoma	*MIR19A*	Gene/Protein
829	Retinoblastoma	*WRN*	Gene/Protein
830	Retinoblastoma	*CCNB2*	Gene/Protein
831	Retinoblastoma	*KDM1A*	Gene/Protein
832	Retinoblastoma	*ARID3A*	Gene/Protein
833	Retinoblastoma	*ENO3*	Gene/Protein
834	Retinoblastoma	*PCDH11X*	Gene/Protein
835	Retinoblastoma	*SPOCD1*	Gene/Protein
836	Retinoblastoma	*AHR*	Gene/Protein
837	Retinoblastoma	*OLIG2*	Gene/Protein
838	Retinoblastoma	*RNMT*	Gene/Protein
839	Retinoblastoma	*MYCBP*	Gene/Protein
840	Retinoblastoma	*PIAS4*	Gene/Protein
841	Retinoblastoma	*SLC6A15*	Gene/Protein
842	Retinoblastoma	*RAB33B*	Gene/Protein
843	Retinoblastoma	*PPP1R15B*	Gene/Protein
844	Retinoblastoma	*PIWIL4*	Gene/Protein
845	Retinoblastoma	*CNST*	Gene/Protein
846	Retinoblastoma	*HSPB2*	Gene/Protein
847	Retinoblastoma	*ORC5*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
848	Retinoblastoma	*RUNX3*	Gene/Protein
849	Retinoblastoma	*PPM1D*	Gene/Protein
850	Retinoblastoma	*HIST2H2AC*	Gene/Protein
851	Retinoblastoma	*HIST2H2AA3*	Gene/Protein
852	Retinoblastoma	*FOXG1*	Gene/Protein
853	Retinoblastoma	*SPHK2*	Gene/Protein
854	Retinoblastoma	*ATP5A1*	Gene/Protein
855	Retinoblastoma	*PARP14*	Gene/Protein
856	Retinoblastoma	*SLC24A4*	Gene/Protein
857	Retinoblastoma	*DGCR8*	Gene/Protein
858	Retinoblastoma	*BAX*	Gene/Protein
859	Retinoblastoma	*EMD*	Gene/Protein
860	Retinoblastoma	*CCNT1*	Gene/Protein
861	Retinoblastoma	*CASP8AP2*	Gene/Protein
862	Retinoblastoma	*CASC1*	Gene/Protein
863	Retinoblastoma	*PPP1R9A*	Gene/Protein
864	Retinoblastoma	*TMEM132D*	Gene/Protein
865	Retinoblastoma	*RPL23*	Gene/Protein
866	Retinoblastoma	*TOX4*	Gene/Protein
867	Retinoblastoma	*MYO16*	Gene/Protein
868	Retinoblastoma	*LAMA1*	Gene/Protein
869	Retinoblastoma	*SLC15A5*	Gene/Protein
870	Retinoblastoma	*FADD*	Gene/Protein
871	Retinoblastoma	*SLC7A14*	Gene/Protein
872	Retinoblastoma	*FOXF2*	Gene/Protein
873	Retinoblastoma	*ID2*	Gene/Protein
874	Retinoblastoma	*RSC1A1*	Gene/Protein
875	Retinoblastoma	*BAP1*	Gene/Protein
876	Retinoblastoma	*CHGA*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
877	Retinoblastoma	*RACGAP1*	Gene/Protein
878	Retinoblastoma	*MT-ND4*	Gene/Protein
879	Retinoblastoma	*XPO1*	Gene/Protein
880	Retinoblastoma	*GNB1*	Gene/Protein
881	Retinoblastoma	*ZFYVE16*	Gene/Protein
882	Retinoblastoma	*SLCO4A1*	Gene/Protein
883	Retinoblastoma	*ELFN1*	Gene/Protein
884	Retinoblastoma	*SERPINF1*	Gene/Protein
885	Retinoblastoma	*TRPC5*	Gene/Protein
886	Retinoblastoma	*WDR81*	Gene/Protein
887	Retinoblastoma	*GPRC6A*	Gene/Protein
888	Retinoblastoma	*CD276*	Gene/Protein
889	Retinoblastoma	*NFIB*	Gene/Protein
890	Retinoblastoma	*AATK*	Gene/Protein
891	Retinoblastoma	*AKAP11*	Gene/Protein
892	Retinoblastoma	*UBE3A*	Gene/Protein
893	Retinoblastoma	*INCENP*	Gene/Protein
894	Retinoblastoma	*MAPK14*	Gene/Protein
895	Retinoblastoma	*STK11*	Gene/Protein
896	Retinoblastoma	*IKZF1*	Gene/Protein
897	Retinoblastoma	*ASGR1*	Gene/Protein
898	Retinoblastoma	*CRYAA*	Gene/Protein
899	Retinoblastoma	*GHRHR*	Gene/Protein
900	Retinoblastoma	*GPR12*	Gene/Protein
901	Retinoblastoma	*TAX1BP1*	Gene/Protein
902	Retinoblastoma	*FARP1*	Gene/Protein
903	Retinoblastoma	*KDM5B*	Gene/Protein
904	Retinoblastoma	*B4GALNT1*	Gene/Protein
905	Retinoblastoma	*SLC25A1*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
906	Retinoblastoma	*MAML1*	Gene/Protein
907	Retinoblastoma	*IH*	Gene/Protein
908	Retinoblastoma	*ACP1*	Gene/Protein
909	Retinoblastoma	*SLC9A5*	Gene/Protein
910	Retinoblastoma	*VPS54*	Gene/Protein
911	Retinoblastoma	*WDR77*	Gene/Protein
912	Retinoblastoma	*RELA*	Gene/Protein
913	Retinoblastoma	*SLC14A1*	Gene/Protein
914	Retinoblastoma	*LINC-ROR*	Gene/Protein
915	Retinoblastoma	*MIR21*	Gene/Protein
916	Retinoblastoma	*SIRT1*	Gene/Protein
917	Retinoblastoma	*SNRPE*	Gene/Protein
918	Retinoblastoma	*PFKFB4*	Gene/Protein
919	Retinoblastoma	*PPP1CC*	Gene/Protein
920	Retinoblastoma	*TFAP2B*	Gene/Protein
921	Retinoblastoma	*ING4*	Gene/Protein
922	Retinoblastoma	*PPP1R12C*	Gene/Protein
923	Retinoblastoma	*ARFGEF3*	Gene/Protein
924	Retinoblastoma	*SHCBP1*	Gene/Protein
925	Retinoblastoma	*SLC44A5*	Gene/Protein
926	Retinoblastoma	*TACR1*	Gene/Protein
927	Retinoblastoma	*AXIN1*	Gene/Protein
928	Retinoblastoma	*CDO1*	Gene/Protein
929	Retinoblastoma	*NOVA1*	Gene/Protein
930	Retinoblastoma	*PPP1R3C*	Gene/Protein
931	Retinoblastoma	*CIB2*	Gene/Protein
932	Retinoblastoma	*RRP1B*	Gene/Protein
933	Retinoblastoma	*TRIM59*	Gene/Protein
934	Retinoblastoma	*LUCAT1*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
935	Retinoblastoma	*STMN1*	Gene/Protein
936	Retinoblastoma	*PPP1R12A*	Gene/Protein
937	Retinoblastoma	*LATS2*	Gene/Protein
938	Retinoblastoma	*CAPN5*	Gene/Protein
939	Retinoblastoma	*ELF4*	Gene/Protein
940	Retinoblastoma	*UBE2L3*	Gene/Protein
941	Retinoblastoma	*PPP2R4*	Gene/Protein
942	Retinoblastoma	*ORC1*	Gene/Protein
943	Retinoblastoma	*DIRAS3*	Gene/Protein
944	Retinoblastoma	*THOC1*	Gene/Protein
945	Retinoblastoma	*LRIG3*	Gene/Protein
946	Retinoblastoma	*LCK*	Gene/Protein
947	Retinoblastoma	*VIS1*	Gene/Protein
948	Retinoblastoma	*PPP1R16B*	Gene/Protein
949	Retinoblastoma	*PCIF1*	Gene/Protein
950	Retinoblastoma	*SLFN11*	Gene/Protein
951	Retinoblastoma	*PTPN13*	Gene/Protein
952	Retinoblastoma	*NAA10*	Gene/Protein
953	Retinoblastoma	*NOC2L*	Gene/Protein
954	Retinoblastoma	*PRMT6*	Gene/Protein
955	Retinoblastoma	*FOXO1*	Gene/Protein
956	Retinoblastoma	*PRDM1*	Gene/Protein
957	Retinoblastoma	*PPP1R12B*	Gene/Protein
958	Retinoblastoma	*TCAP*	Gene/Protein
959	Retinoblastoma	*LMTK2*	Gene/Protein
960	Retinoblastoma	*CHCHD3*	Gene/Protein
961	Retinoblastoma	*ARID1A*	Gene/Protein
962	Retinoblastoma	*PPA1*	Gene/Protein
963	Retinoblastoma	*MAP1LC3A*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
964	Retinoblastoma	*EED*	Gene/Protein
965	Retinoblastoma	*WDHD1*	Gene/Protein
966	Retinoblastoma	*ZNF654*	Gene/Protein
967	Retinoblastoma	*CADM2*	Gene/Protein
968	Retinoblastoma	*C21orf2*	Gene/Protein
969	Retinoblastoma	*URI1*	Gene/Protein
970	Retinoblastoma	*TOLLIP*	Gene/Protein
971	Retinoblastoma	*HES1*	Gene/Protein
972	Retinoblastoma	*UBR5*	Gene/Protein
973	Retinoblastoma	*EZR*	Gene/Protein
974	Retinoblastoma	*SIX6*	Gene/Protein
975	Retinoblastoma	*CAMSAP3*	Gene/Protein
976	Retinoblastoma	*PRDM14*	Gene/Protein
977	Retinoblastoma	*JAK3*	Gene/Protein
978	Retinoblastoma	*NR2F2*	Gene/Protein
979	Retinoblastoma	*MED12*	Gene/Protein
980	Retinoblastoma	*CCNG1*	Gene/Protein
981	Retinoblastoma	*PPP1R13B*	Gene/Protein
982	Retinoblastoma	*CEP192*	Gene/Protein
983	Retinoblastoma	*CCDC8*	Gene/Protein
984	Retinoblastoma	*DMTF1*	Gene/Protein
985	Retinoblastoma	*CTSZ*	Gene/Protein
986	Retinoblastoma	*ANKRD36B*	Gene/Protein
987	Retinoblastoma	*AKTIP*	Gene/Protein
988	Retinoblastoma	*HOXA11-AS*	Gene/Protein
989	Retinoblastoma	*CD9*	Gene/Protein
990	Retinoblastoma	*CACUL1*	Gene/Protein
991	Retinoblastoma	*GSPT1*	Gene/Protein
992	Retinoblastoma	*PHRF1*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
993	Retinoblastoma	*VMP1*	Gene/Protein
994	Retinoblastoma	*LMTK3*	Gene/Protein
995	Retinoblastoma	*RAD21*	Gene/Protein
996	Retinoblastoma	*EPHB2*	Gene/Protein
997	Retinoblastoma	*RPS6*	Gene/Protein
998	Retinoblastoma	*MYO1D*	Gene/Protein
999	Retinoblastoma	*STK38*	Gene/Protein
1000	Retinoblastoma	*HSP90AA1*	Gene/Protein
1001	Retinoblastoma	*PBX3*	Gene/Protein
1002	Retinoblastoma	*CDK19*	Gene/Protein
1003	Retinoblastoma	*SYTL2*	Gene/Protein
1004	Retinoblastoma	*DUSP22*	Gene/Protein
1005	Retinoblastoma	*STC1*	Gene/Protein
1006	Retinoblastoma	*MNAT1*	Gene/Protein
1007	Retinoblastoma	*PIGF*	Gene/Protein
1008	Retinoblastoma	*INADL*	Gene/Protein
1009	Retinoblastoma	*CHCHD2*	Gene/Protein
1010	Retinoblastoma	*TET1*	Gene/Protein
1011	Retinoblastoma	*BLZF1*	Gene/Protein
1012	Retinoblastoma	*CTBP1*	Gene/Protein
1013	Retinoblastoma	*KCNA6*	Gene/Protein
1014	Retinoblastoma	*RFC2*	Gene/Protein
1015	Retinoblastoma	*ELL*	Gene/Protein
1016	Retinoblastoma	*MIRLET7E*	Gene/Protein
1017	Retinoblastoma	*MSH3*	Gene/Protein
1018	Retinoblastoma	*SETD1A*	Gene/Protein
1019	Retinoblastoma	*ABCC1*	Gene/Protein
1020	Retinoblastoma	*APC2*	Gene/Protein
1021	Retinoblastoma	*SGK3*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1022	Retinoblastoma	*ZBTB38*	Gene/Protein
1023	Retinoblastoma	*CYCSP5*	Gene/Protein
1024	Retinoblastoma	*NF2*	Gene/Protein
1025	Retinoblastoma	*RAD51*	Gene/Protein
1026	Retinoblastoma	*CDK16*	Gene/Protein
1027	Retinoblastoma	*SFI1*	Gene/Protein
1028	Retinoblastoma	*PPP1R3B*	Gene/Protein
1029	Retinoblastoma	*ABL1*	Gene/Protein
1030	Retinoblastoma	*SYT1*	Gene/Protein
1031	Retinoblastoma	*CDKN2C*	Gene/Protein
1032	Retinoblastoma	*AHCYL1*	Gene/Protein
1033	Retinoblastoma	*TRDMT1*	Gene/Protein
1034	Retinoblastoma	*PARD6A*	Gene/Protein
1035	Retinoblastoma	*FAM20C*	Gene/Protein
1036	Retinoblastoma	*TBC1D9*	Gene/Protein
1037	Retinoblastoma	*ANKRD42*	Gene/Protein
1038	Retinoblastoma	*FAT1*	Gene/Protein
1039	Retinoblastoma	*POU3F3*	Gene/Protein
1040	Retinoblastoma	*ABCE1*	Gene/Protein
1041	Retinoblastoma	*SRSF10*	Gene/Protein
1042	Retinoblastoma	*NACC1*	Gene/Protein
1043	Retinoblastoma	*BRCA1*	Gene/Protein
1044	Retinoblastoma	*NKX2-1*	Gene/Protein
1045	Retinoblastoma	*NEUROD1*	Gene/Protein
1046	Retinoblastoma	*DYNC1H1*	Gene/Protein
1047	Retinoblastoma	*HYDIN*	Gene/Protein
1048	Retinoblastoma	*IL1B*	Gene/Protein
1049	Retinoblastoma	*ZEB2*	Gene/Protein
1050	Retinoblastoma	*ASPH*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1051	Retinoblastoma	*SPRY1*	Gene/Protein
1052	Retinoblastoma	*DDX3X*	Gene/Protein
1053	Retinoblastoma	*PRKCQ*	Gene/Protein
1054	Retinoblastoma	*PSMD4*	Gene/Protein
1055	Retinoblastoma	*SIAH1*	Gene/Protein
1056	Retinoblastoma	*KAT2A*	Gene/Protein
1057	Retinoblastoma	*MAD2L1*	Gene/Protein
1058	Retinoblastoma	*CFLAR*	Gene/Protein
1059	Retinoblastoma	*PLIN3*	Gene/Protein
1060	Retinoblastoma	*IGF1R*	Gene/Protein
1061	Retinoblastoma	*HCP5*	Gene/Protein
1062	Retinoblastoma	*GPX7*	Gene/Protein
1063	Retinoblastoma	*RS1*	Gene/Protein
1064	Retinoblastoma	*TRA2B*	Gene/Protein
1065	Retinoblastoma	*CDH17*	Gene/Protein
1066	Retinoblastoma	*SPZ1*	Gene/Protein
1067	Retinoblastoma	*FOXP1*	Gene/Protein
1068	Retinoblastoma	*TTF1*	Gene/Protein
1069	Retinoblastoma	*TP63*	Gene/Protein
1070	Retinoblastoma	*GNB3*	Gene/Protein
1071	Retinoblastoma	*SH3GLB1*	Gene/Protein
1072	Retinoblastoma	*ANXA5*	Gene/Protein
1073	Retinoblastoma	*LHX1*	Gene/Protein
1074	Retinoblastoma	*C10orf2*	Gene/Protein
1075	Retinoblastoma	*GPHA2*	Gene/Protein
1076	Retinoblastoma	*OCRL*	Gene/Protein
1077	Retinoblastoma	*RPS18*	Gene/Protein
1078	Retinoblastoma	*SGCA*	Gene/Protein
1079	Retinoblastoma	*SMARCC1*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1080	Retinoblastoma	*YY1AP1*	Gene/Protein
1081	Retinoblastoma	*AP2M1*	Gene/Protein
1082	Retinoblastoma	*HNRNPL*	Gene/Protein
1083	Retinoblastoma	*ASH2L*	Gene/Protein
1084	Retinoblastoma	*PBK*	Gene/Protein
1085	Retinoblastoma	*PCDH15*	Gene/Protein
1086	Retinoblastoma	*KMT2B*	Gene/Protein
1087	Retinoblastoma	*TRPM7*	Gene/Protein
1088	Retinoblastoma	*RBM10*	Gene/Protein
1089	Retinoblastoma	*ABCC3*	Gene/Protein
1090	Retinoblastoma	*NSUN2*	Gene/Protein
1091	Retinoblastoma	*CISD1*	Gene/Protein
1092	Retinoblastoma	*NUP62*	Gene/Protein
1093	Retinoblastoma	*TFAP2A*	Gene/Protein
1094	Retinoblastoma	*KLF5*	Gene/Protein
1095	Retinoblastoma	*DCN*	Gene/Protein
1096	Retinoblastoma	*TIMP2*	Gene/Protein
1097	Retinoblastoma	*MLH1*	Gene/Protein
1098	Retinoblastoma	*VNN1*	Gene/Protein
1099	Retinoblastoma	*RPGRIP1L*	Gene/Protein
1100	Retinoblastoma	*PREX2*	Gene/Protein
1101	Retinoblastoma	*KHDRBS1*	Gene/Protein
1102	Retinoblastoma	*BTG1*	Gene/Protein
1103	Retinoblastoma	*SLC39A5*	Gene/Protein
1104	Retinoblastoma	*H2AFZ*	Gene/Protein
1105	Retinoblastoma	*CHDM*	Gene/Protein
1106	Retinoblastoma	*GADD45G*	Gene/Protein
1107	Retinoblastoma	*OPN3*	Gene/Protein
1108	Retinoblastoma	*KDM2B*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1109	Retinoblastoma	*TRIM28*	Gene/Protein
1110	Retinoblastoma	*EGF*	Gene/Protein
1111	Retinoblastoma	*ING2*	Gene/Protein
1112	Retinoblastoma	*MPHOSPH10*	Gene/Protein
1113	Retinoblastoma	*PTPRT*	Gene/Protein
1114	Retinoblastoma	*NRF1*	Gene/Protein
1115	Retinoblastoma	*SAG*	Gene/Protein
1116	Retinoblastoma	*PDGFB*	Gene/Protein
1117	Retinoblastoma	*BMND7*	Gene/Protein
1118	Retinoblastoma	*BMND8*	Gene/Protein
1119	Retinoblastoma	*SULF1*	Gene/Protein
1120	Retinoblastoma	*PTK2*	Gene/Protein
1121	Retinoblastoma	*GATA6*	Gene/Protein
1122	Retinoblastoma	*EIF2AK2*	Gene/Protein
1123	Retinoblastoma	*TRPM1*	Gene/Protein
1124	Retinoblastoma	*PEA15*	Gene/Protein
1125	Retinoblastoma	*SLC39A1*	Gene/Protein
1126	Retinoblastoma	*NKX6-2*	Gene/Protein
1127	Retinoblastoma	*MGEA5*	Gene/Protein
1128	Retinoblastoma	*SMARCB1*	Gene/Protein
1129	Retinoblastoma	*DLG3*	Gene/Protein
1130	Retinoblastoma	*CALCOCO2*	Gene/Protein
1131	Retinoblastoma	*NUSAP1*	Gene/Protein
1132	Retinoblastoma	*CEMIP*	Gene/Protein
1133	Retinoblastoma	*EPHA3*	Gene/Protein
1134	Retinoblastoma	*PIK3R3*	Gene/Protein
1135	Retinoblastoma	*VAV3*	Gene/Protein
1136	Retinoblastoma	*SQSTM1*	Gene/Protein
1137	Retinoblastoma	*SLC9A9*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1138	Retinoblastoma	*MCM3*	Gene/Protein
1139	Retinoblastoma	*SALL1*	Gene/Protein
1140	Retinoblastoma	*PPP1R14A*	Gene/Protein
1141	Retinoblastoma	*HFM1*	Gene/Protein
1142	Retinoblastoma	*KDR*	Gene/Protein
1143	Retinoblastoma	*FGF7*	Gene/Protein
1144	Retinoblastoma	*NFYA*	Gene/Protein
1145	Retinoblastoma	*SLC25A25*	Gene/Protein
1146	Retinoblastoma	*WNT4*	Gene/Protein
1147	Retinoblastoma	*GJC1*	Gene/Protein
1148	Retinoblastoma	*HRASLS*	Gene/Protein
1149	Retinoblastoma	*POLA1*	Gene/Protein
1150	Retinoblastoma	*SHOX2*	Gene/Protein
1151	Retinoblastoma	*PCDH7*	Gene/Protein
1152	Retinoblastoma	*TRIP13*	Gene/Protein
1153	Retinoblastoma	*DKK2*	Gene/Protein
1154	Retinoblastoma	*ARR3*	Gene/Protein
1155	Retinoblastoma	*TBX1*	Gene/Protein
1156	Retinoblastoma	*PLAGL1*	Gene/Protein
1157	Retinoblastoma	*CNTN2*	Gene/Protein
1159	Retinoblastoma	*TRPM2*	Gene/Protein
1160	Retinoblastoma	*ATM*	Gene/Protein
1161	Retinoblastoma	*ZBTB7A*	Gene/Protein
1162	Retinoblastoma	*WIPF2*	Gene/Protein
1163	Retinoblastoma	*MZB1*	Gene/Protein
1164	Retinoblastoma	*JARID2*	Gene/Protein
1165	Retinoblastoma	*ESR1*	Gene/Protein
1166	Retinoblastoma	*SLC1A5*	Gene/Protein
1167	Retinoblastoma	*UCHL1*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1168	Retinoblastoma	*TOP2A*	Gene/Protein
1169	Retinoblastoma	*SLPI*	Gene/Protein
1170	Retinoblastoma	*STAU1*	Gene/Protein
1171	Retinoblastoma	*REC8*	Gene/Protein
1172	Retinoblastoma	*MAD2L2*	Gene/Protein
1173	Retinoblastoma	*PGM1*	Gene/Protein
1174	Retinoblastoma	*RCOR1*	Gene/Protein
1175	Retinoblastoma	*ENO1*	Gene/Protein
1176	Retinoblastoma	*RASGRF1*	Gene/Protein
1177	Retinoblastoma	*POLD3*	Gene/Protein
1178	Retinoblastoma	*GLI3*	Gene/Protein
1179	Retinoblastoma	*JAK2*	Gene/Protein
1180	Retinoblastoma	*TP53BP1*	Gene/Protein
1181	Retinoblastoma	*CXADR*	Gene/Protein
1182	Retinoblastoma	*RPL11*	Gene/Protein
1183	Retinoblastoma	*SND1*	Gene/Protein
1184	Retinoblastoma	*RPA2*	Gene/Protein
1185	Retinoblastoma	*SUN2*	Gene/Protein
1186	Retinoblastoma	*BIRC7*	Gene/Protein
1187	Retinoblastoma	*NFKB2*	Gene/Protein
1188	Retinoblastoma	*HLA-DPA1*	Gene/Protein
1189	Retinoblastoma	*FANCI*	Gene/Protein
1190	Retinoblastoma	*TIMP1*	Gene/Protein
1191	Retinoblastoma	*PIK3R2*	Gene/Protein
1192	Retinoblastoma	*KIF23*	Gene/Protein
1193	Retinoblastoma	*SLC25A15*	Gene/Protein
1194	Retinoblastoma	*HSPH1*	Gene/Protein
1195	Retinoblastoma	*MAPKAP1*	Gene/Protein
1196	Retinoblastoma	*WNT1*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1197	Retinoblastoma	*RB1CC1*	Gene/Protein
1198	Retinoblastoma	*NKX6-1*	Gene/Protein
1199	Retinoblastoma	*BRD4*	Gene/Protein
1200	Retinoblastoma	*RPS6KB1*	Gene/Protein
1201	Retinoblastoma	*KIF18A*	Gene/Protein
1202	Retinoblastoma	*SLC17A8*	Gene/Protein
1203	Retinoblastoma	*IL10*	Gene/Protein
1204	Retinoblastoma	*PKMYT1*	Gene/Protein
1205	Retinoblastoma	*AKAP9*	Gene/Protein
1206	Retinoblastoma	*FTL*	Gene/Protein
1207	Retinoblastoma	*SNAI2*	Gene/Protein
1208	Retinoblastoma	*ATF4*	Gene/Protein
1209	Retinoblastoma	*LTF*	Gene/Protein
1210	Retinoblastoma	*ABCC4*	Gene/Protein
1211	Retinoblastoma	*BID*	Gene/Protein
1212	Retinoblastoma	*CD24*	Gene/Protein
1213	Retinoblastoma	*MAP2*	Gene/Protein
1214	Retinoblastoma	*MAGI1*	Gene/Protein
1215	Retinoblastoma	*EGLN2*	Gene/Protein
1216	Retinoblastoma	*HCFC1*	Gene/Protein
1217	Retinoblastoma	*CHD8*	Gene/Protein
1218	Retinoblastoma	*FAM72B*	Gene/Protein
1219	Retinoblastoma	*STAT5A*	Gene/Protein
1220	Retinoblastoma	*TDGF1*	Gene/Protein
1221	Retinoblastoma	*TRIB1*	Gene/Protein
1222	Retinoblastoma	*GJA4*	Gene/Protein
1223	Retinoblastoma	*PPP1R11*	Gene/Protein
1224	Retinoblastoma	*CASC5*	Gene/Protein
1225	Retinoblastoma	*LMNB2*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1226	Retinoblastoma	*ALB*	Gene/Protein
1227	Retinoblastoma	*ACKR3*	Gene/Protein
1228	Retinoblastoma	*SLC26A2*	Gene/Protein
1229	Retinoblastoma	*NRIP1*	Gene/Protein
1230	Retinoblastoma	*MSI2*	Gene/Protein
1231	Retinoblastoma	*SLC24A5*	Gene/Protein
1232	Retinoblastoma	*BNIP3L*	Gene/Protein
1233	Retinoblastoma	*IL1RAP*	Gene/Protein
1234	Retinoblastoma	*CHAF1A*	Gene/Protein
1235	Retinoblastoma	*SMYD3*	Gene/Protein
1236	Retinoblastoma	*COASY*	Gene/Protein
1237	Retinoblastoma	*ALAS2*	Gene/Protein
1238	Retinoblastoma	*ZFYVE1*	Gene/Protein
1239	Retinoblastoma	*SLC25A21*	Gene/Protein
1240	Retinoblastoma	*STAT5B*	Gene/Protein
1241	Retinoblastoma	*CDC37*	Gene/Protein
1242	Retinoblastoma	*ADCYAP1*	Gene/Protein
1243	Retinoblastoma	*SPRY2*	Gene/Protein
1244	Retinoblastoma	*KAT6B*	Gene/Protein
1245	Retinoblastoma	*KCNK10*	Gene/Protein
1246	Retinoblastoma	*DDIT3*	Gene/Protein
1247	Retinoblastoma	*VAPB*	Gene/Protein
1248	Retinoblastoma	*NAA15*	Gene/Protein
1249	Retinoblastoma	*SETD8*	Gene/Protein
1250	Retinoblastoma	*NTRK1*	Gene/Protein
1251	Retinoblastoma	*PRKAB1*	Gene/Protein
1252	Retinoblastoma	*CREB1*	Gene/Protein
1253	Retinoblastoma	*HOXA1*	Gene/Protein
1254	Retinoblastoma	*MYF6*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1255	Retinoblastoma	*TFF2*	Gene/Protein
1256	Retinoblastoma	*MAP2K3*	Gene/Protein
1257	Retinoblastoma	*MAP2K6*	Gene/Protein
1258	Retinoblastoma	*ZC3H12A*	Gene/Protein
1259	Retinoblastoma	*RSPO1*	Gene/Protein
1260	Retinoblastoma	*PRKAA2*	Gene/Protein
1261	Retinoblastoma	*TCF4*	Gene/Protein
1262	Retinoblastoma	*TRIM31*	Gene/Protein
1263	Retinoblastoma	*SIN3A*	Gene/Protein
1264	Retinoblastoma	*DIABLO*	Gene/Protein
1265	Retinoblastoma	*RICTOR*	Gene/Protein
1266	Retinoblastoma	*NUMA1*	Gene/Protein
1267	Retinoblastoma	*ILK*	Gene/Protein
1268	Retinoblastoma	*PRKAA1*	Gene/Protein
1269	Retinoblastoma	*CNPY2*	Gene/Protein
1270	Retinoblastoma	*PAX9*	Gene/Protein
1271	Retinoblastoma	*HOTTIP*	Gene/Protein
1272	Retinoblastoma	*RNF2*	Gene/Protein
1273	Retinoblastoma	*FUT8*	Gene/Protein
1274	Retinoblastoma	*WNT7B*	Gene/Protein
1275	Retinoblastoma	*ITK*	Gene/Protein
1276	Retinoblastoma	*CSMD1*	Gene/Protein
1277	Retinoblastoma	*EIF4E*	Gene/Protein
1278	Retinoblastoma	*RSF1*	Gene/Protein
1279	Retinoblastoma	*PKN1*	Gene/Protein
1280	Retinoblastoma	*ESRRB*	Gene/Protein
1281	Retinoblastoma	*HDAC2*	Gene/Protein
1282	Retinoblastoma	*SMURF2*	Gene/Protein
1283	Retinoblastoma	*RAN*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1284	Retinoblastoma	*SLC45A1*	Gene/Protein
1285	Retinoblastoma	*HLA-DRA*	Gene/Protein
1286	Retinoblastoma	*KCNH1*	Gene/Protein
1287	Retinoblastoma	*FGFR3*	Gene/Protein
1288	Retinoblastoma	*RARB*	Gene/Protein
1289	Retinoblastoma	*ERBB3*	Gene/Protein
1290	Retinoblastoma	*CDT1*	Gene/Protein
1291	Retinoblastoma	*CLCN7*	Gene/Protein
1292	Retinoblastoma	*SERPINB2*	Gene/Protein
1293	Retinoblastoma	*TIAM1*	Gene/Protein
1294	Retinoblastoma	*CUL1*	Gene/Protein
1295	Retinoblastoma	*HAT1*	Gene/Protein
1296	Retinoblastoma	*NCL*	Gene/Protein
1297	Retinoblastoma	*DMP1*	Gene/Protein
1298	Retinoblastoma	*NUP98*	Gene/Protein
1299	Retinoblastoma	*MIB1*	Gene/Protein
1300	Retinoblastoma	*NCAPG*	Gene/Protein
1301	Retinoblastoma	*PAK1*	Gene/Protein
1302	Retinoblastoma	*PRKCB*	Gene/Protein
1303	Retinoblastoma	*IFT88*	Gene/Protein
1304	Retinoblastoma	*NFE2L1*	Gene/Protein
1305	Retinoblastoma	*DLG2*	Gene/Protein
1306	Retinoblastoma	*CHD4*	Gene/Protein
1307	Retinoblastoma	*SLC27A5*	Gene/Protein
1308	Retinoblastoma	*PDCD10*	Gene/Protein
1309	Retinoblastoma	*ADK*	Gene/Protein
1310	Retinoblastoma	*HMGB2*	Gene/Protein
1311	Retinoblastoma	*DMC1*	Gene/Protein
1312	Retinoblastoma	*ARID2*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1313	Retinoblastoma	*MGMT*	Gene/Protein
1314	Retinoblastoma	*DLG1*	Gene/Protein
1315	Retinoblastoma	*RFC1*	Gene/Protein
1316	Retinoblastoma	*VDAC2*	Gene/Protein
1317	Retinoblastoma	*PEMT*	Gene/Protein
1318	Retinoblastoma	*JUND*	Gene/Protein
1319	Retinoblastoma	*KPNA2*	Gene/Protein
1320	Retinoblastoma	*POLE3*	Gene/Protein
1321	Retinoblastoma	*SPRED1*	Gene/Protein
1322	Retinoblastoma	*PNPLA2*	Gene/Protein
1323	Retinoblastoma	*DVL2*	Gene/Protein
1324	Retinoblastoma	*ITLN1*	Gene/Protein
1325	Retinoblastoma	*PADI2*	Gene/Protein
1326	Retinoblastoma	*IL11*	Gene/Protein
1327	Retinoblastoma	*IGF2BP1*	Gene/Protein
1328	Retinoblastoma	*PCDH8*	Gene/Protein
1329	Retinoblastoma	*HCAR3*	Gene/Protein
1330	Retinoblastoma	*GTPBP4*	Gene/Protein
1331	Retinoblastoma	*NUDT1*	Gene/Protein
1332	Retinoblastoma	*SETD7*	Gene/Protein
1333	Retinoblastoma	*FOXF1*	Gene/Protein
1334	Retinoblastoma	*PBX1*	Gene/Protein
1335	Retinoblastoma	*LOXL1*	Gene/Protein
1336	Retinoblastoma	*HDAC7*	Gene/Protein
1337	Retinoblastoma	*TYK2*	Gene/Protein
1338	Retinoblastoma	*WNT2*	Gene/Protein
1339	Retinoblastoma	*MTA1*	Gene/Protein
1340	Retinoblastoma	*IFNAR2*	Gene/Protein
1341	Retinoblastoma	*SMAD6*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1342	Retinoblastoma	*PSCA*	Gene/Protein
1343	Retinoblastoma	*RBFOX1*	Gene/Protein
1344	Retinoblastoma	*SLC43A1*	Gene/Protein
1345	Retinoblastoma	*EXT1*	Gene/Protein
1346	Retinoblastoma	*GRB10*	Gene/Protein
1347	Retinoblastoma	*PVRL1*	Gene/Protein
1348	Retinoblastoma	*TRIM33*	Gene/Protein
1349	Retinoblastoma	*SSTR5*	Gene/Protein
1350	Retinoblastoma	*WWC1*	Gene/Protein
1351	Retinoblastoma	*HID1*	Gene/Protein
1352	Retinoblastoma	*PI3*	Gene/Protein
1353	Retinoblastoma	*SLC6A6*	Gene/Protein
1354	Retinoblastoma	*NONO*	Gene/Protein
1355	Retinoblastoma	*SFPQ*	Gene/Protein
1356	Retinoblastoma	*HSPB8*	Gene/Protein
1357	Retinoblastoma	*ITGA1*	Gene/Protein
1358	Retinoblastoma	*SLC26A1*	Gene/Protein
1359	Retinoblastoma	*MYO5A*	Gene/Protein
1360	Retinoblastoma	*CADM1*	Gene/Protein
1361	Retinoblastoma	*TIMP3*	Gene/Protein
1362	Retinoblastoma	*IFNB1*	Gene/Protein
1363	Retinoblastoma	*H3F3B*	Gene/Protein
1364	Retinoblastoma	*PPARGC1A*	Gene/Protein
1365	Retinoblastoma	*PDE6B*	Gene/Protein
1366	Retinoblastoma	*RANP1*	Gene/Protein
1367	Retinoblastoma	*RAC1*	Gene/Protein
1368	Retinoblastoma	*CNN1*	Gene/Protein
1369	Retinoblastoma	*GALT*	Gene/Protein
1370	Retinoblastoma	*KDM4A*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1371	Retinoblastoma	*KCNA5*	Gene/Protein
1372	Retinoblastoma	*FUS*	Gene/Protein
1373	Retinoblastoma	*RPL5*	Gene/Protein
1374	Retinoblastoma	*TXN2*	Gene/Protein
1375	Retinoblastoma	*SACS*	Gene/Protein
1376	Retinoblastoma	*LRP1B*	Gene/Protein
1377	Retinoblastoma	*MSX2*	Gene/Protein
1378	Retinoblastoma	*ELOVL6*	Gene/Protein
1379	Retinoblastoma	*PTCH1*	Gene/Protein
1380	Retinoblastoma	*PPARA*	Gene/Protein
1381	Retinoblastoma	*EWSR1*	Gene/Protein
1382	Retinoblastoma	*GATA1*	Gene/Protein
1383	Retinoblastoma	*KIR2DL3*	Gene/Protein
1384	Retinoblastoma	*ACACB*	Gene/Protein
1385	Retinoblastoma	*EMP1*	Gene/Protein
1386	Retinoblastoma	*PLIN2*	Gene/Protein
1387	Retinoblastoma	*SSRP1*	Gene/Protein
1388	Retinoblastoma	*DROSHA*	Gene/Protein
1389	Retinoblastoma	*DAPK2*	Gene/Protein
1390	Retinoblastoma	*APP*	Gene/Protein
1391	Retinoblastoma	*KAT5*	Gene/Protein
1392	Retinoblastoma	*MIR15B*	Gene/Protein
1393	Retinoblastoma	*MAP1B*	Gene/Protein
1394	Retinoblastoma	*CARM1*	Gene/Protein
1395	Retinoblastoma	*PAX5*	Gene/Protein
1396	Retinoblastoma	*PLAG1*	Gene/Protein
1397	Retinoblastoma	*SLC7A11*	Gene/Protein
1398	Retinoblastoma	*PREP*	Gene/Protein
1399	Retinoblastoma	*DESI2*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1400	Retinoblastoma	*ASPN*	Gene/Protein
1401	Retinoblastoma	*CLN3*	Gene/Protein
1402	Retinoblastoma	*RTCA*	Gene/Protein
1403	Retinoblastoma	*TCF3*	Gene/Protein
1404	Retinoblastoma	*PKP2*	Gene/Protein
1405	Retinoblastoma	*SLC44A1*	Gene/Protein
1406	Retinoblastoma	*SRA1*	Gene/Protein
1407	Retinoblastoma	*SMC1A*	Gene/Protein
1408	Retinoblastoma	*SLC7A7*	Gene/Protein
1409	Retinoblastoma	*LRP1*	Gene/Protein
1410	Retinoblastoma	*HDAC4*	Gene/Protein
1411	Retinoblastoma	*SLC25A5*	Gene/Protein
1412	Retinoblastoma	*ASPM*	Gene/Protein
1413	Retinoblastoma	*UCN*	Gene/Protein
1414	Retinoblastoma	*SLC7A13*	Gene/Protein
1415	Retinoblastoma	*SF3B1*	Gene/Protein
1416	Retinoblastoma	*TP73*	Gene/Protein
1417	Retinoblastoma	*SHH*	Gene/Protein
1418	Retinoblastoma	*LRIG1*	Gene/Protein
1419	Retinoblastoma	*GFAP*	Gene/Protein
1420	Retinoblastoma	*CAPN1*	Gene/Protein
1421	Retinoblastoma	*CD82*	Gene/Protein
1422	Retinoblastoma	*SOX5*	Gene/Protein
1423	Retinoblastoma	*KCNH8*	Gene/Protein
1424	Retinoblastoma	*UBA1*	Gene/Protein
1425	Retinoblastoma	*IKZF3*	Gene/Protein
1426	Retinoblastoma	*XRCC4*	Gene/Protein
1427	Retinoblastoma	*EPHA4*	Gene/Protein
1428	Retinoblastoma	*ADAM17*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1429	Retinoblastoma	*SLC38A5*	Gene/Protein
1430	Retinoblastoma	*CDH15*	Gene/Protein
1431	Retinoblastoma	*TNFSF9*	Gene/Protein
1432	Retinoblastoma	*LOX*	Gene/Protein
1433	Retinoblastoma	*DLGAP5*	Gene/Protein
1434	Retinoblastoma	*SLC7A10*	Gene/Protein
1435	Retinoblastoma	*GSTA1*	Gene/Protein
1436	Retinoblastoma	*PPARGC1B*	Gene/Protein
1437	Retinoblastoma	*METAP2*	Gene/Protein
1438	Retinoblastoma	*SART3*	Gene/Protein
1439	Retinoblastoma	*MAPK10*	Gene/Protein
1440	Retinoblastoma	*CIRBP*	Gene/Protein
1441	Retinoblastoma	*DCLK1*	Gene/Protein
1442	Retinoblastoma	*RET*	Gene/Protein
1443	Retinoblastoma	*MYOD1*	Gene/Protein
1444	Retinoblastoma	*GRM7*	Gene/Protein
1445	Retinoblastoma	*FOXO3*	Gene/Protein
1446	Retinoblastoma	*ELK1*	Gene/Protein
1447	Retinoblastoma	*CYP3A*	Gene/Protein
1448	Retinoblastoma	*DLL1*	Gene/Protein
1449	Retinoblastoma	*ACLY*	Gene/Protein
1450	Retinoblastoma	*KMT2D*	Gene/Protein
1451	Retinoblastoma	*CD44*	Gene/Protein
1452	Retinoblastoma	*UPF1*	Gene/Protein
1453	Retinoblastoma	*CD81*	Gene/Protein
1454	Retinoblastoma	*SIRT6*	Gene/Protein
1455	Retinoblastoma	*CNGB1*	Gene/Protein
1456	Retinoblastoma	*GJA5*	Gene/Protein
1457	Retinoblastoma	*WDR5*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1458	Retinoblastoma	*FASN*	Gene/Protein
1459	Retinoblastoma	*FOXC2*	Gene/Protein
1460	Retinoblastoma	*NCOA4*	Gene/Protein
1461	Retinoblastoma	*SLC4A4*	Gene/Protein
1462	Retinoblastoma	*UBD*	Gene/Protein
1463	Retinoblastoma	*MIR100*	Gene/Protein
1464	Retinoblastoma	*DIO3*	Gene/Protein
1465	Retinoblastoma	*PPP1R8*	Gene/Protein
1466	Retinoblastoma	*SORL1*	Gene/Protein
1467	Retinoblastoma	*MCOLN1*	Gene/Protein
1468	Retinoblastoma	*SIRT3*	Gene/Protein
1469	Retinoblastoma	*MAPK1*	Gene/Protein
1470	Retinoblastoma	*FOS*	Gene/Protein
1471	Retinoblastoma	*SPN*	Gene/Protein
1472	Retinoblastoma	*NCOA2*	Gene/Protein
1473	Retinoblastoma	*HK2*	Gene/Protein
1474	Retinoblastoma	*DUX4L2*	Gene/Protein
1475	Retinoblastoma	*REL*	Gene/Protein
1476	Retinoblastoma	*MIR25*	Gene/Protein
1477	Retinoblastoma	*YAP1*	Gene/Protein
1478	Retinoblastoma	*MDK*	Gene/Protein
1479	Retinoblastoma	*FTSJ1*	Gene/Protein
1480	Retinoblastoma	*CDK12*	Gene/Protein
1481	Retinoblastoma	*GYPA*	Gene/Protein
1482	Retinoblastoma	*PLCL1*	Gene/Protein
1483	Retinoblastoma	*MIR27B*	Gene/Protein
1484	Retinoblastoma	*ADAM10*	Gene/Protein
1485	Retinoblastoma	*IL4*	Gene/Protein
1486	Retinoblastoma	*SLC46A1*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1487	Retinoblastoma	*TEK*	Gene/Protein
1488	Retinoblastoma	*ROR2*	Gene/Protein
1489	Retinoblastoma	*LOR*	Gene/Protein
1490	Retinoblastoma	*DUX4L1*	Gene/Protein
1491	Retinoblastoma	*WFS1*	Gene/Protein
1492	Retinoblastoma	*MKL1*	Gene/Protein
1493	Retinoblastoma	*NR4A3*	Gene/Protein
1494	Retinoblastoma	*DUX4*	Gene/Protein
1495	Retinoblastoma	*ATOH1*	Gene/Protein
1496	Retinoblastoma	*NOTCH4*	Gene/Protein
1497	Retinoblastoma	*PIK3CG*	Gene/Protein
1498	Retinoblastoma	*SOX6*	Gene/Protein
1499	Retinoblastoma	*PCA3*	Gene/Protein
1500	Retinoblastoma	*ASXL1*	Gene/Protein
1501	Retinoblastoma	*VCP*	Gene/Protein
1502	Retinoblastoma	*SYNE1*	Gene/Protein
1503	Retinoblastoma	*LGMN*	Gene/Protein
1504	Retinoblastoma	*LGALS3*	Gene/Protein
1505	Retinoblastoma	*MT-ND6*	Gene/Protein
1506	Retinoblastoma	*MXI1*	Gene/Protein
1507	Retinoblastoma	*MSH2*	Gene/Protein
1508	Retinoblastoma	*TNC*	Gene/Protein
1509	Retinoblastoma	*MAP3K1*	Gene/Protein
1510	Retinoblastoma	*REST*	Gene/Protein
1511	Retinoblastoma	*EBF1*	Gene/Protein
1512	Retinoblastoma	*KCNA1*	Gene/Protein
1513	Retinoblastoma	*IL17RB*	Gene/Protein
1514	Retinoblastoma	*BMP4*	Gene/Protein
1515	Retinoblastoma	*CACNA1G*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1516	Retinoblastoma	*MTR*	Gene/Protein
1517	Retinoblastoma	*S100A1*	Gene/Protein
1518	Retinoblastoma	*SETDB1*	Gene/Protein
1519	Retinoblastoma	*NSD1*	Gene/Protein
1520	Retinoblastoma	*EIF1*	Gene/Protein
1521	Retinoblastoma	*CAT*	Gene/Protein
1522	Retinoblastoma	*TEAD1*	Gene/Protein
1523	Retinoblastoma	*GLS*	Gene/Protein
1524	Retinoblastoma	*FGF9*	Gene/Protein
1525	Retinoblastoma	*MSRA*	Gene/Protein
1526	Retinoblastoma	*MRPL36*	Gene/Protein
1527	Retinoblastoma	*PPP1R15A*	Gene/Protein
1528	Retinoblastoma	*SIRT7*	Gene/Protein
1528	Retinoblastoma	*IL13*	Gene/Protein
1529	Retinoblastoma	*SLC7A4*	Gene/Protein
1530	Retinoblastoma	*UBE2I*	Gene/Protein
1531	Retinoblastoma	*NCOR1*	Gene/Protein
1532	Retinoblastoma	*IL4R*	Gene/Protein
1533	Retinoblastoma	*UCP3*	Gene/Protein
1534	Retinoblastoma	*HK1*	Gene/Protein
1535	Retinoblastoma	*PPP3CA*	Gene/Protein
1536	Retinoblastoma	*PPP1R1B*	Gene/Protein
1537	Retinoblastoma	*NPC2*	Gene/Protein
1538	Retinoblastoma	*FBXW7*	Gene/Protein
1539	Retinoblastoma	*UBE2K*	Gene/Protein
1540	Retinoblastoma	*CYP19A1*	Gene/Protein
1541	Retinoblastoma	*CDH13*	Gene/Protein
1542	Retinoblastoma	*ID3*	Gene/Protein
1543	Retinoblastoma	*RBPJ*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1544	Retinoblastoma	*CUX1*	Gene/Protein
1545	Retinoblastoma	*APOBEC3A*	Gene/Protein
1546	Retinoblastoma	*TRIB3*	Gene/Protein
1547	Retinoblastoma	*HSPB6*	Gene/Protein
1548	Retinoblastoma	*CD70*	Gene/Protein
1549	Retinoblastoma	*NEK2*	Gene/Protein
1550	Retinoblastoma	*PTGER1*	Gene/Protein
1551	Retinoblastoma	*BRD2*	Gene/Protein
1552	Retinoblastoma	*CLEC7A*	Gene/Protein
1553	Retinoblastoma	*SLC7A5*	Gene/Protein
1554	Retinoblastoma	*MYH11*	Gene/Protein
1555	Retinoblastoma	*UBE2S*	Gene/Protein
1556	Retinoblastoma	*YTHDF1*	Gene/Protein
1557	Retinoblastoma	*SFRP2*	Gene/Protein
1558	Retinoblastoma	*PFKM*	Gene/Protein
1559	Retinoblastoma	*BSG*	Gene/Protein
1560	Retinoblastoma	*MSX1*	Gene/Protein
1561	Retinoblastoma	*CD4*	Gene/Protein
1562	Retinoblastoma	*ITGA5*	Gene/Protein
1563	Retinoblastoma	*SPI1*	Gene/Protein
1564	Retinoblastoma	*IL2*	Gene/Protein
1565	Retinoblastoma	*ITPR2*	Gene/Protein
1566	Retinoblastoma	*SHC1*	Gene/Protein
1567	Retinoblastoma	*NLRP2*	Gene/Protein
1568	Retinoblastoma	*SOX11*	Gene/Protein
1569	Retinoblastoma	*GLB1*	Gene/Protein
1570	Retinoblastoma	*PRKAR1A*	Gene/Protein
1571	Retinoblastoma	*TRPV4*	Gene/Protein
1572	Retinoblastoma	*NOX4*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1573	Retinoblastoma	*SLC22A5*	Gene/Protein
1574	Retinoblastoma	*APEX1*	Gene/Protein
1575	Retinoblastoma	*ACOX1*	Gene/Protein
1576	Retinoblastoma	*TNFRSF9*	Gene/Protein
1577	Retinoblastoma	*KRT20*	Gene/Protein
1578	Retinoblastoma	*LCP1*	Gene/Protein
1579	Retinoblastoma	*TYROBP*	Gene/Protein
1580	Retinoblastoma	*FEN1*	Gene/Protein
1581	Retinoblastoma	*MAP2K2*	Gene/Protein
1582	Retinoblastoma	*MIR107*	Gene/Protein
1583	Retinoblastoma	*GREM1*	Gene/Protein
1584	Retinoblastoma	*DNM1L*	Gene/Protein
1585	Retinoblastoma	*GATA4*	Gene/Protein
1586	Retinoblastoma	*BBC3*	Gene/Protein
1587	Retinoblastoma	*SLC7A6*	Gene/Protein
1588	Retinoblastoma	*TNFRSF10B*	Gene/Protein
1589	Retinoblastoma	*GPNMB*	Gene/Protein
1590	Retinoblastoma	*BRCA2*	Gene/Protein
1591	Retinoblastoma	*TPMT*	Gene/Protein
1592	Retinoblastoma	*SLC27A1*	Gene/Protein
1593	Retinoblastoma	*IKBKB*	Gene/Protein
1594	Retinoblastoma	*SCAP*	Gene/Protein
1595	Retinoblastoma	*OGT*	Gene/Protein
1596	Retinoblastoma	*SH2D2A*	Gene/Protein
1597	Retinoblastoma	*IL32*	Gene/Protein
1598	Retinoblastoma	*SCGB1D1*	Gene/Protein
1599	Retinoblastoma	*UGT1A1*	Gene/Protein
1600	Retinoblastoma	*RPS19*	Gene/Protein
1601	Retinoblastoma	*KITLG*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1602	Retinoblastoma	*KLF6*	Gene/Protein
1603	Retinoblastoma	*NANOS1*	Gene/Protein
1604	Retinoblastoma	*HOOK2*	Gene/Protein
1605	Retinoblastoma	*CSE1L*	Gene/Protein
1606	Retinoblastoma	*PVR*	Gene/Protein
1607	Retinoblastoma	*CD53*	Gene/Protein
1608	Retinoblastoma	*NEFL*	Gene/Protein
1609	Retinoblastoma	*CXCL14*	Gene/Protein
1610	Retinoblastoma	*ARHGAP9*	Gene/Protein
1611	Retinoblastoma	*DOT1L*	Gene/Protein
1612	Retinoblastoma	*C21orf33*	Gene/Protein
1613	Retinoblastoma	*TGFBI*	Gene/Protein
1614	Retinoblastoma	*NAA50*	Gene/Protein
1615	Retinoblastoma	*SLC4A1*	Gene/Protein
1616	Retinoblastoma	*SLU7*	Gene/Protein
1617	Retinoblastoma	*NBN*	Gene/Protein
1618	Retinoblastoma	*IL17A*	Gene/Protein
1619	Retinoblastoma	*OR7E66P*	Gene/Protein
1620	Retinoblastoma	*CASP2*	Gene/Protein
1621	Retinoblastoma	*IL6*	Gene/Protein
1622	Retinoblastoma	*IL3*	Gene/Protein
1623	Retinoblastoma	*TPX2*	Gene/Protein
1624	Retinoblastoma	*ITGA4*	Gene/Protein
1625	Retinoblastoma	*PSIP1*	Gene/Protein
1626	Retinoblastoma	*PKM*	Gene/Protein
1627	Retinoblastoma	*KRT10*	Gene/Protein
1628	Retinoblastoma	*IVL*	Gene/Protein
1629	Retinoblastoma	*CTAG1B*	Gene/Protein
1630	Retinoblastoma	*FGFR1*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1631	Retinoblastoma	*SMAD5*	Gene/Protein
1632	Retinoblastoma	*MROS*	Gene/Protein
1633	Retinoblastoma	*PDGFRB*	Gene/Protein
1634	Retinoblastoma	*BIRC2*	Gene/Protein
1635	Retinoblastoma	*ARHGEF5*	Gene/Protein
1636	Retinoblastoma	*CEBPB*	Gene/Protein
1637	Retinoblastoma	*IGFBP3*	Gene/Protein
1638	Retinoblastoma	*RECK*	Gene/Protein
1639	Retinoblastoma	*GAPDH*	Gene/Protein
1640	Retinoblastoma	*KLF4*	Gene/Protein
1641	Retinoblastoma	*MYF5*	Gene/Protein
1642	Retinoblastoma	*DDIT4*	Gene/Protein
1643	Retinoblastoma	*RARA*	Gene/Protein
1644	Retinoblastoma	*EXO1*	Gene/Protein
1645	Retinoblastoma	*TNF*	Gene/Protein
1646	Retinoblastoma	*THM*	Gene/Protein
1647	Retinoblastoma	*MLXIPL*	Gene/Protein
1648	Retinoblastoma	*SLC47A1*	Gene/Protein
1649	Retinoblastoma	*PLAUR*	Gene/Protein
1650	Retinoblastoma	*NOS2*	Gene/Protein
1651	Retinoblastoma	*CDX2*	Gene/Protein
1652	Retinoblastoma	*XRCC5*	Gene/Protein
1653	Retinoblastoma	*IL2RG*	Gene/Protein
1654	Retinoblastoma	*GSDMA*	Gene/Protein
1655	Retinoblastoma	*DUSP12*	Gene/Protein
1656	Retinoblastoma	*CD47*	Gene/Protein
1657	Retinoblastoma	*GHRH*	Gene/Protein
1658	Retinoblastoma	*CYP2A*	Gene/Protein
1659	Retinoblastoma	*BAG3*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1660	Retinoblastoma	*CAV1*	Gene/Protein
1661	Retinoblastoma	*BGN*	Gene/Protein
1662	Retinoblastoma	*MIR22*	Gene/Protein
1663	Retinoblastoma	*TSG101*	Gene/Protein
1664	Retinoblastoma	*SLC22A3*	Gene/Protein
1665	Retinoblastoma	*GPM6A*	Gene/Protein
1666	Retinoblastoma	*CNTF*	Gene/Protein
1667	Retinoblastoma	*TGFB2*	Gene/Protein
1668	Retinoblastoma	*CACNA1H*	Gene/Protein
1669	Retinoblastoma	*MAPK3*	Gene/Protein
1670	Retinoblastoma	*HOXA9*	Gene/Protein
1671	Retinoblastoma	*NOTCH3*	Gene/Protein
1672	Retinoblastoma	*XRCC6*	Gene/Protein
1673	Retinoblastoma	*DNMT3A*	Gene/Protein
1674	Retinoblastoma	*IL24*	Gene/Protein
1675	Retinoblastoma	*IGF2BP3*	Gene/Protein
1676	Retinoblastoma	*DEFA1B*	Gene/Protein
1677	Retinoblastoma	*ERCC2*	Gene/Protein
1678	Retinoblastoma	*PPIA*	Gene/Protein
1679	Retinoblastoma	*LDHA*	Gene/Protein
1680	Retinoblastoma	*SLC33A1*	Gene/Protein
1681	Retinoblastoma	*GDF2*	Gene/Protein
1682	Retinoblastoma	*FCER2*	Gene/Protein
1683	Retinoblastoma	*MYBPC3*	Gene/Protein
1684	Retinoblastoma	*HNRNPK*	Gene/Protein
1685	Retinoblastoma	*HDAC8*	Gene/Protein
1686	Retinoblastoma	*SATB2*	Gene/Protein
1687	Retinoblastoma	*ARNT*	Gene/Protein
1688	Retinoblastoma	*IRF5*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1689	Retinoblastoma	*CBX5*	Gene/Protein
1690	Retinoblastoma	*PDGFRA*	Gene/Protein
1691	Retinoblastoma	*ZBTB16*	Gene/Protein
1692	Retinoblastoma	*FH*	Gene/Protein
1693	Retinoblastoma	*SOX17*	Gene/Protein
1694	Retinoblastoma	*HGF*	Gene/Protein
1695	Retinoblastoma	*IDH1*	Gene/Protein
1696	Retinoblastoma	*ATXN1*	Gene/Protein
1697	Retinoblastoma	*TCN2*	Gene/Protein
1698	Retinoblastoma	*RHOA*	Gene/Protein
1699	Retinoblastoma	*PFKFB3*	Gene/Protein
1700	Retinoblastoma	*MAPK7*	Gene/Protein
1701	Retinoblastoma	*KIF11*	Gene/Protein
1702	Retinoblastoma	*STIP1*	Gene/Protein
1703	Retinoblastoma	*TLR4*	Gene/Protein
1704	Retinoblastoma	*ID1*	Gene/Protein
1705	Retinoblastoma	*SLC13A5*	Gene/Protein
1706	Retinoblastoma	*PDK4*	Gene/Protein
1707	Retinoblastoma	*MSH6*	Gene/Protein
1708	Retinoblastoma	*LGALS4*	Gene/Protein
1709	Retinoblastoma	*SPATA2*	Gene/Protein
1710	Retinoblastoma	*SAMHD1*	Gene/Protein
1711	Retinoblastoma	*DEFA1*	Gene/Protein
1712	Retinoblastoma	*HLA-DPB1*	Gene/Protein
1713	Retinoblastoma	*GLI1*	Gene/Protein
1714	Retinoblastoma	*KIT*	Gene/Protein
1715	Retinoblastoma	*FGF1*	Gene/Protein
1716	Retinoblastoma	*TAGLN*	Gene/Protein
1717	Retinoblastoma	*HDAC6*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1718	Retinoblastoma	*F13A1*	Gene/Protein
1719	Retinoblastoma	*FKBP4*	Gene/Protein
1720	Retinoblastoma	*NQO1*	Gene/Protein
1721	Retinoblastoma	*VCAN*	Gene/Protein
1722	Retinoblastoma	*CLDN7*	Gene/Protein
1723	Retinoblastoma	*SMARCA2*	Gene/Protein
1724	Retinoblastoma	*MCU*	Gene/Protein
1725	Retinoblastoma	*INS*	Gene/Protein
1726	Retinoblastoma	*F2*	Gene/Protein
1727	Retinoblastoma	*GRB2*	Gene/Protein
1728	Retinoblastoma	*NOG*	Gene/Protein
1729	Retinoblastoma	*PITX2*	Gene/Protein
1730	Retinoblastoma	*PTH*	Gene/Protein
1731	Retinoblastoma	*RBFOX3*	Gene/Protein
1732	Retinoblastoma	*OPTN*	Gene/Protein
1733	Retinoblastoma	*MUC4*	Gene/Protein
1734	Retinoblastoma	*RELN*	Gene/Protein
1735	Retinoblastoma	*LONP1*	Gene/Protein
1736	Retinoblastoma	*ITGA2B*	Gene/Protein
1737	Retinoblastoma	*PARD3*	Gene/Protein
1738	Retinoblastoma	*DLL4*	Gene/Protein
1739	Retinoblastoma	*CA1*	Gene/Protein
1740	Retinoblastoma	*AKT3*	Gene/Protein
1741	Retinoblastoma	*EIF2S2*	Gene/Protein
1742	Retinoblastoma	*BAK1*	Gene/Protein
1743	Retinoblastoma	*THEG*	Gene/Protein
1744	Retinoblastoma	*ARTN*	Gene/Protein
1745	Retinoblastoma	*AREG*	Gene/Protein
1746	Retinoblastoma	*IFIT3*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1747	Retinoblastoma	*CD63*	Gene/Protein
1748	Retinoblastoma	*GADD45A*	Gene/Protein
1749	Retinoblastoma	*ACVRL1*	Gene/Protein
1750	Retinoblastoma	*PRKD2*	Gene/Protein
1751	Retinoblastoma	*CD68*	Gene/Protein
1752	Retinoblastoma	*NTN1*	Gene/Protein
1753	Retinoblastoma	*CRTC1*	Gene/Protein
1754	Retinoblastoma	*PTS*	Gene/Protein
1755	Retinoblastoma	*ADIPOQ*	Gene/Protein
1756	Retinoblastoma	*NOS3*	Gene/Protein
1757	Retinoblastoma	*AMPH*	Gene/Protein
1758	Retinoblastoma	*CXCR1*	Gene/Protein
1759	Retinoblastoma	*CEL*	Gene/Protein
1760	Retinoblastoma	*LAMP1*	Gene/Protein
1761	Retinoblastoma	*SLC12A5*	Gene/Protein
1762	Retinoblastoma	*RUNX2*	Gene/Protein
1763	Retinoblastoma	*ZFYVE9*	Gene/Protein
1764	Retinoblastoma	*CRY2*	Gene/Protein
1765	Retinoblastoma	*IGF2*	Gene/Protein
1766	Retinoblastoma	*CD274*	Gene/Protein
1767	Retinoblastoma	*KRT5*	Gene/Protein
1768	Retinoblastoma	*PVT1*	Gene/Protein
1769	Retinoblastoma	*MIR146A*	Gene/Protein
1770	Retinoblastoma	*TNFRSF10A*	Gene/Protein
1771	Retinoblastoma	*LIG4*	Gene/Protein
1772	Retinoblastoma	*LILRB1*	Gene/Protein
1773	Retinoblastoma	*MAPT*	Gene/Protein
1774	Retinoblastoma	*CLDN1*	Gene/Protein
1775	Retinoblastoma	*CNOT6*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1776	Retinoblastoma	*FABP4*	Gene/Protein
1777	Retinoblastoma	*RASSF1*	Gene/Protein
1778	Retinoblastoma	*FOXA2*	Gene/Protein
1779	Retinoblastoma	*GRM1*	Gene/Protein
1780	Retinoblastoma	*TOP1*	Gene/Protein
1781	Retinoblastoma	*TRAF3*	Gene/Protein
1782	Retinoblastoma	*SLC9C1*	Gene/Protein
1783	Retinoblastoma	*GAP43*	Gene/Protein
1784	Retinoblastoma	*FBN1*	Gene/Protein
1785	Retinoblastoma	*TXNIP*	Gene/Protein
1786	Retinoblastoma	*SLC6A2*	Gene/Protein
1787	Retinoblastoma	*MT-ATP6*	Gene/Protein
1788	Retinoblastoma	*PRKCA*	Gene/Protein
1789	Retinoblastoma	*HMGCR*	Gene/Protein
1790	Retinoblastoma	*DUSP1*	Gene/Protein
1791	Retinoblastoma	*FGF19*	Gene/Protein
1792	Retinoblastoma	*SOX9*	Gene/Protein
1793	Retinoblastoma	*CALB1*	Gene/Protein
1794	Retinoblastoma	*CENPA*	Gene/Protein
1795	Retinoblastoma	*GCG*	Gene/Protein
1796	Retinoblastoma	*BCL6*	Gene/Protein
1797	Retinoblastoma	*TGFB1*	Gene/Protein
1798	Retinoblastoma	*PNPLA3*	Gene/Protein
1799	Retinoblastoma	*CD40LG*	Gene/Protein
1800	Retinoblastoma	*TRPM8*	Gene/Protein
1801	Retinoblastoma	*IL6R*	Gene/Protein
1802	Retinoblastoma	*MMP11*	Gene/Protein
1803	Retinoblastoma	*APOBEC3B*	Gene/Protein
1804	Retinoblastoma	*SLC5A1*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1805	Retinoblastoma	*MGP*	Gene/Protein
1806	Retinoblastoma	*BDNF*	Gene/Protein
1807	Retinoblastoma	*LIPA*	Gene/Protein
1808	Retinoblastoma	*SYCE1L*	Gene/Protein
1809	Retinoblastoma	*CYTIP*	Gene/Protein
1810	Retinoblastoma	*CDC20*	Gene/Protein
1811	Retinoblastoma	*COL18A1*	Gene/Protein
1812	Retinoblastoma	*UCP2*	Gene/Protein
1813	Retinoblastoma	*ATIC*	Gene/Protein
1814	Retinoblastoma	*SOST*	Gene/Protein
1815	Retinoblastoma	*BRIP1*	Gene/Protein
1816	Retinoblastoma	*RYR1*	Gene/Protein
1817	Retinoblastoma	*SCFV*	Gene/Protein
1818	Retinoblastoma	*THY1*	Gene/Protein
1819	Retinoblastoma	*CYCS*	Gene/Protein
1820	Retinoblastoma	*H6PD*	Gene/Protein
1821	Retinoblastoma	*EDNRB*	Gene/Protein
1822	Retinoblastoma	*CD99L2*	Gene/Protein
1823	Retinoblastoma	*FASLG*	Gene/Protein
1824	Retinoblastoma	*PROC*	Gene/Protein
1825	Retinoblastoma	*SLC7A1*	Gene/Protein
1826	Retinoblastoma	*ABCG1*	Gene/Protein
1827	Retinoblastoma	*CYP1A1*	Gene/Protein
1828	Retinoblastoma	*CRTAP*	Gene/Protein
1829	Retinoblastoma	*IFNAR1*	Gene/Protein
1830	Retinoblastoma	*GABARAPL1*	Gene/Protein
1831	Retinoblastoma	*SLC8A1*	Gene/Protein
1832	Retinoblastoma	*PMAIP1*	Gene/Protein
1833	Retinoblastoma	*AXIN2*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1834	Retinoblastoma	*NFE2L2*	Gene/Protein
1835	Retinoblastoma	*SLC12A2*	Gene/Protein
1836	Retinoblastoma	*POMC*	Gene/Protein
1837	Retinoblastoma	*KRT14*	Gene/Protein
1838	Retinoblastoma	*MMP1*	Gene/Protein
1839	Retinoblastoma	*TF*	Gene/Protein
1840	Retinoblastoma	*MARK2*	Gene/Protein
1841	Retinoblastoma	*NTF3*	Gene/Protein
1842	Retinoblastoma	*INSR*	Gene/Protein
1843	Retinoblastoma	*CCR4*	Gene/Protein
1844	Retinoblastoma	*NELFCD*	Gene/Protein
1845	Retinoblastoma	*GADD45B*	Gene/Protein
1846	Retinoblastoma	*CDC42*	Gene/Protein
1847	Retinoblastoma	*FLT4*	Gene/Protein
1848	Retinoblastoma	*LEP*	Gene/Protein
1849	Retinoblastoma	*PGR*	Gene/Protein
1850	Retinoblastoma	*MYH6*	Gene/Protein
1851	Retinoblastoma	*CRHR1*	Gene/Protein
1852	Retinoblastoma	*BGLAP*	Gene/Protein
1853	Retinoblastoma	*NCOR2*	Gene/Protein
1854	Retinoblastoma	*EEF1A2*	Gene/Protein
1855	Retinoblastoma	*CASP1*	Gene/Protein
1856	Retinoblastoma	*LRPPRC*	Gene/Protein
1857	Retinoblastoma	*RORA*	Gene/Protein
1858	Retinoblastoma	*CTSL*	Gene/Protein
1859	Retinoblastoma	*ROCK2*	Gene/Protein
1860	Retinoblastoma	*ZGLP1*	Gene/Protein
1861	Retinoblastoma	*APOC3*	Gene/Protein
1862	Retinoblastoma	*SLC16A1*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1863	Retinoblastoma	*CXCL11*	Gene/Protein
1864	Retinoblastoma	*ACPP*	Gene/Protein
1865	Retinoblastoma	*PDHX*	Gene/Protein
1866	Retinoblastoma	*DRD1*	Gene/Protein
1867	Retinoblastoma	*BNIP3*	Gene/Protein
1868	Retinoblastoma	*POU2F1*	Gene/Protein
1869	Retinoblastoma	*NCF1*	Gene/Protein
1870	Retinoblastoma	*ADA*	Gene/Protein
1871	Retinoblastoma	*AFP*	Gene/Protein
1872	Retinoblastoma	*ACAN*	Gene/Protein
1873	Retinoblastoma	*AGT*	Gene/Protein
1874	Retinoblastoma	*AGTR1*	Gene/Protein
1875	Retinoblastoma	*AGTR2*	Gene/Protein
1876	Retinoblastoma	*AHSG*	Gene/Protein
1877	Retinoblastoma	*AKT2*	Gene/Protein
1878	Retinoblastoma	*ALDH1A1*	Gene/Protein
1879	Retinoblastoma	*ALK*	Gene/Protein
1880	Retinoblastoma	*ANGPT2*	Gene/Protein
1881	Retinoblastoma	*ANXA1*	Gene/Protein
1882	Retinoblastoma	*APOA1*	Gene/Protein
1883	Retinoblastoma	*APOE*	Gene/Protein
1884	Retinoblastoma	*KLK3*	Gene/Protein
1885	Retinoblastoma	*ATF3*	Gene/Protein
1886	Retinoblastoma	*ATR*	Gene/Protein
1887	Retinoblastoma	*B2M*	Gene/Protein
1888	Retinoblastoma	*BMP7*	Gene/Protein
1889	Retinoblastoma	*CACNA1C*	Gene/Protein
1890	Retinoblastoma	*CALR*	Gene/Protein
1891	Retinoblastoma	*CASP7*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1892	Retinoblastoma	*CASR*	Gene/Protein
1893	Retinoblastoma	*RUNX1*	Gene/Protein
1894	Retinoblastoma	*CD1A*	Gene/Protein
1895	Retinoblastoma	*CD1B*	Gene/Protein
1896	Retinoblastoma	*CD1C*	Gene/Protein
1897	Retinoblastoma	*CD28*	Gene/Protein
1898	Retinoblastoma	*CD80*	Gene/Protein
1899	Retinoblastoma	*CD86*	Gene/Protein
1900	Retinoblastoma	*CD36*	Gene/Protein
1901	Retinoblastoma	*SCARB1*	Gene/Protein
1902	Retinoblastoma	*SCARB2*	Gene/Protein
1903	Retinoblastoma	*CD38*	Gene/Protein
1904	Retinoblastoma	*CD40*	Gene/Protein
1905	Retinoblastoma	*CD69*	Gene/Protein
1906	Retinoblastoma	*CDH5*	Gene/Protein
1907	Retinoblastoma	*CFTR*	Gene/Protein
1908	Retinoblastoma	*CISH*	Gene/Protein
1909	Retinoblastoma	*CLU*	Gene/Protein
1910	Retinoblastoma	*ABCC2*	Gene/Protein
1911	Retinoblastoma	*CNR2*	Gene/Protein
1912	Retinoblastoma	*COL1A1*	Gene/Protein
1913	Retinoblastoma	*COL2A1*	Gene/Protein
1914	Retinoblastoma	*COMT*	Gene/Protein
1915	Retinoblastoma	*CR2*	Gene/Protein
1916	Retinoblastoma	*CSF1*	Gene/Protein
1917	Retinoblastoma	*CSF2*	Gene/Protein
1918	Retinoblastoma	*CSF3*	Gene/Protein
1919	Retinoblastoma	*CTGF*	Gene/Protein
1920	Retinoblastoma	*CTLA4*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1921	Retinoblastoma	*CTSB*	Gene/Protein
1922	Retinoblastoma	*CTSK*	Gene/Protein
1923	Retinoblastoma	*CYBB*	Gene/Protein
1924	Retinoblastoma	*CYP3A4*	Gene/Protein
1925	Retinoblastoma	*CYP24A1*	Gene/Protein
1926	Retinoblastoma	*CYP27B1*	Gene/Protein
1927	Retinoblastoma	*DECR1*	Gene/Protein
1928	Retinoblastoma	*DMD*	Gene/Protein
1929	Retinoblastoma	*DNAH8*	Gene/Protein
1930	Retinoblastoma	*DRD2*	Gene/Protein
1931	Retinoblastoma	*ELAVL1*	Gene/Protein
1932	Retinoblastoma	*ELN*	Gene/Protein
1933	Retinoblastoma	*ENG*	Gene/Protein
1934	Retinoblastoma	*EPO*	Gene/Protein
1935	Retinoblastoma	*ERBB4*	Gene/Protein
1936	Retinoblastoma	*ETS1*	Gene/Protein
1937	Retinoblastoma	*ETV6*	Gene/Protein
1938	Retinoblastoma	*F3*	Gene/Protein
1939	Retinoblastoma	*FCGR3A*	Gene/Protein
1940	Retinoblastoma	*FCGR3B*	Gene/Protein
1941	Retinoblastoma	*FGF2*	Gene/Protein
1942	Retinoblastoma	*FGFR2*	Gene/Protein
1943	Retinoblastoma	*MLANA*	Gene/Protein
1944	Retinoblastoma	*FLT1*	Gene/Protein
1945	Retinoblastoma	*FLT3*	Gene/Protein
1946	Retinoblastoma	*FN1*	Gene/Protein
1947	Retinoblastoma	*FRZB*	Gene/Protein
1948	Retinoblastoma	*FUT3*	Gene/Protein
1949	Retinoblastoma	*G6PD*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1950	Retinoblastoma	*GABPA*	Gene/Protein
1951	Retinoblastoma	*GATA2*	Gene/Protein
1952	Retinoblastoma	*GATA3*	Gene/Protein
1953	Retinoblastoma	*MSTN*	Gene/Protein
1954	Retinoblastoma	*GDNF*	Gene/Protein
1955	Retinoblastoma	*GJA1*	Gene/Protein
1956	Retinoblastoma	*GLI2*	Gene/Protein
1957	Retinoblastoma	*GLP1R*	Gene/Protein
1958	Retinoblastoma	*GLUL*	Gene/Protein
1959	Retinoblastoma	*GNAS*	Gene/Protein
1960	Retinoblastoma	*CXCR3*	Gene/Protein
1961	Retinoblastoma	*GPX4*	Gene/Protein
1962	Retinoblastoma	*GRM5*	Gene/Protein
1963	Retinoblastoma	*CXCL1*	Gene/Protein
1964	Retinoblastoma	*CXCL2*	Gene/Protein
1965	Retinoblastoma	*GSK3B*	Gene/Protein
1966	Retinoblastoma	*GSTM1*	Gene/Protein
1967	Retinoblastoma	*GSTP1*	Gene/Protein
1968	Retinoblastoma	*CFH*	Gene/Protein
1969	Retinoblastoma	*HLA-DRB1*	Gene/Protein
1970	Retinoblastoma	*HLA-DRB4*	Gene/Protein
1971	Retinoblastoma	*HMOX1*	Gene/Protein
1972	Retinoblastoma	*FOXA1*	Gene/Protein
1973	Retinoblastoma	*HNRNPC*	Gene/Protein
1974	Retinoblastoma	*HSPA5*	Gene/Protein
1975	Retinoblastoma	*HSPA8*	Gene/Protein
1976	Retinoblastoma	*HSPD1*	Gene/Protein
1977	Retinoblastoma	*HTR2A*	Gene/Protein
1978	Retinoblastoma	*ICAM1*	Gene/Protein

Table 4.1:List of genes of retinoblastoma (Continued).

Sr. No.	**Disease**	**Gene Name**	**Assoication Name**
1979	Retinoblastoma	*IDH2*	Gene/Protein
1980	Retinoblastoma	*IFNG*	Gene/Protein
1981	Retinoblastoma	*IL1A*	Gene/Protein
1982	Retinoblastoma	*CXCL8*	Gene/Protein
1983	Retinoblastoma	*IL15*	Gene/Protein
1984	Retinoblastoma	*CXCL10*	Gene/Protein
1985	Retinoblastoma	*INSRR*	Gene/Protein
1986	Retinoblastoma	*PDX1*	Gene/Protein
1987	Retinoblastoma	*IRS1*	Gene/Protein
1988	Retinoblastoma	*ITGB1*	Gene/Protein
1989	Retinoblastoma	*ITPR1*	Gene/Protein
1990	Retinoblastoma	*JAK1*	Gene/Protein
1991	Retinoblastoma	*KCNQ1*	Gene/Protein
1992	Retinoblastoma	*KISS1*	Gene/Protein
1993	Retinoblastoma	*KRT18*	Gene/Protein
1994	Retinoblastoma	*LIF*	Gene/Protein
1995	Retinoblastoma	*LTBR*	Gene/Protein
1996	Retinoblastoma	*NBR1*	Gene/Protein
1997	Retinoblastoma	*SMAD3*	Gene/Protein
1998	Retinoblastoma	*MC4R*	Gene/Protein
1999	Retinoblastoma	*MECP2*	Gene/Protein
2000	Retinoblastoma	*CD99*	Gene/Protein

4.2 Network Building

Accessing the STRING database and entering a list of 2000 retinoblastoma genes were both required steps. *Homo sapiens* was selected as organism. A network that included 1870 nodes was subsequently established as a result of this (Fig 4.1).

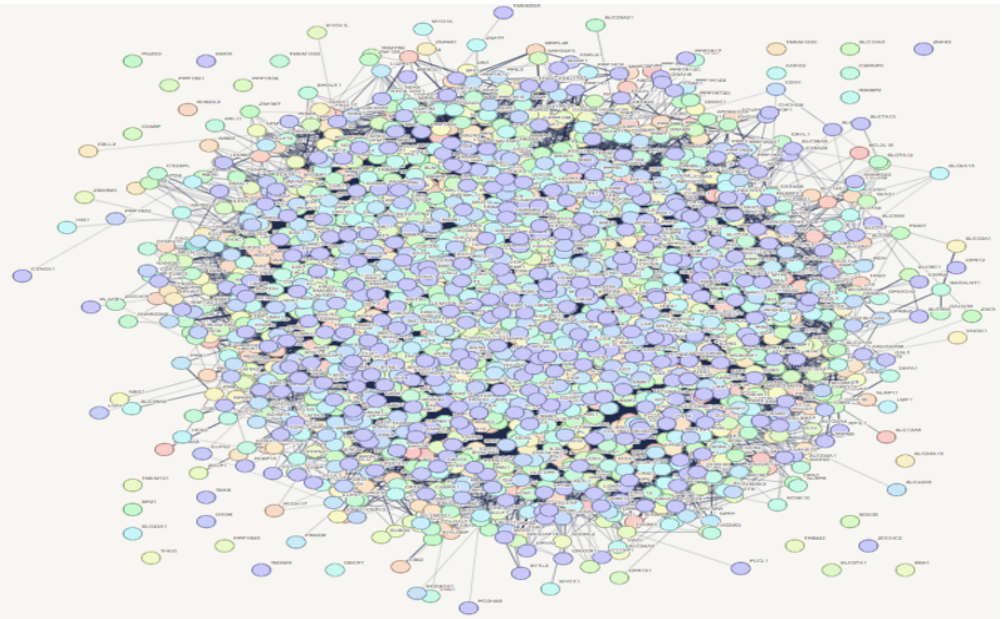


FIGURE 4.1: Network of 2000 genes.

4.3 Cluster Generation

Subsequently, the process entailed the formation of clusters. To achieve this, selection of clusters was done and then proceeded to perform K-means clustering. The number of clusters was incrementally adjusted starting from 3, 4, 5, 6, and so on, and then implemented. Clusters ranging from 3 to 25 were verified based on the KEGG pathway. Within the KEGG pathway, a total of 38 pathways related to retinoblastoma were identified. Across all 38 pathways, clusters ranging from 3 to 25 were verified (Fig 4.2). The clusters generated are shown in the (Table 4.2).

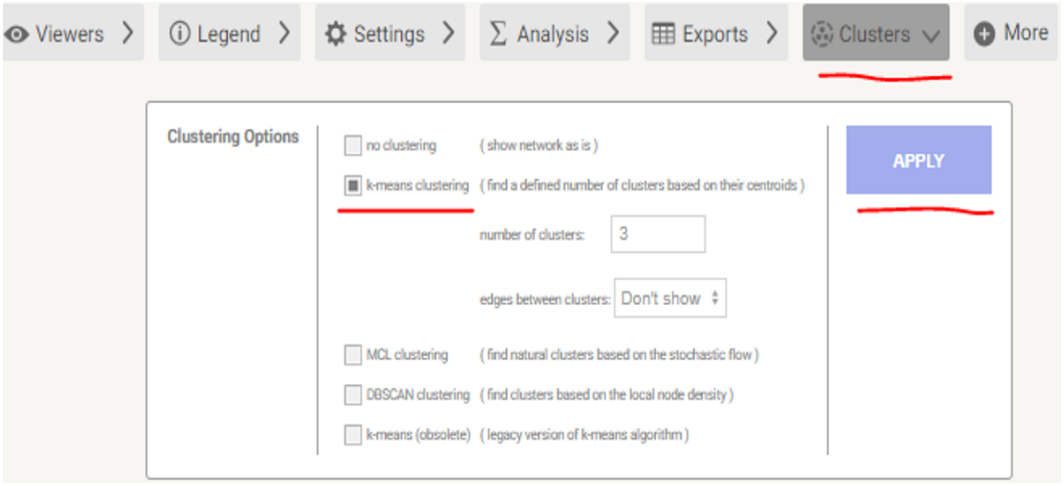


FIGURE 4.2: Executing K-means clustering.

TABLE 4.2: Cluster structures formed after K-means clustering.

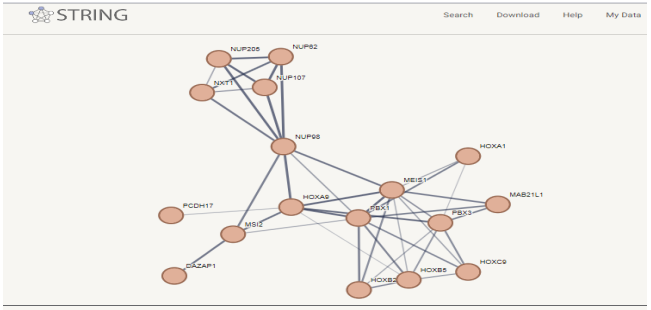
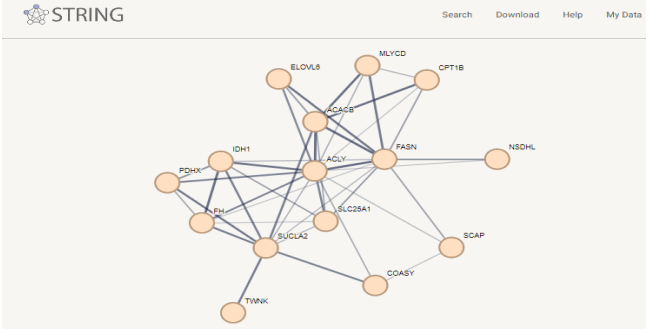
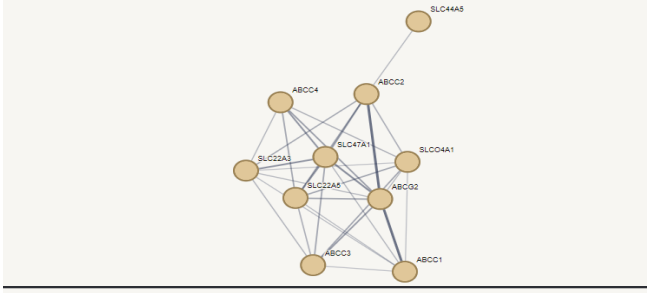
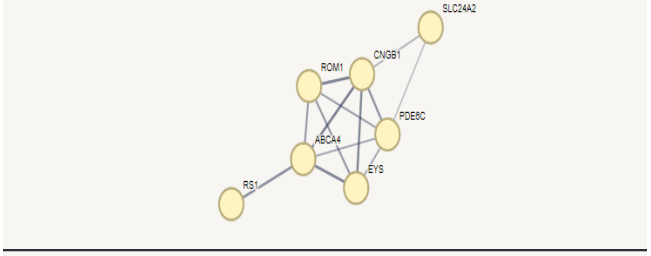
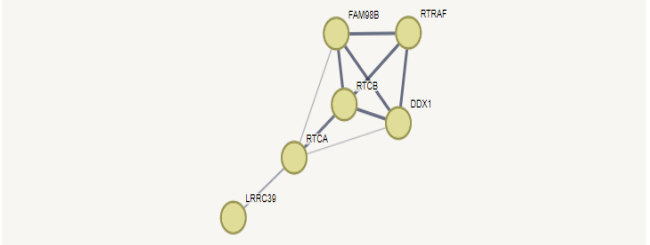
Sr. No.	Cluster No.	Cluster Structure
1	3	
2	4	
3	5	
4	6	
5	7	

Table 4.2: Cluster structures (Continued).

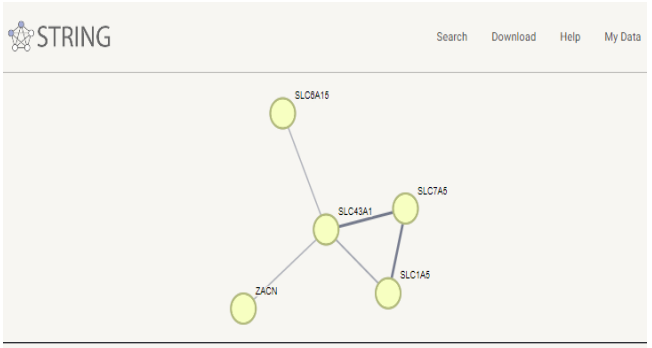
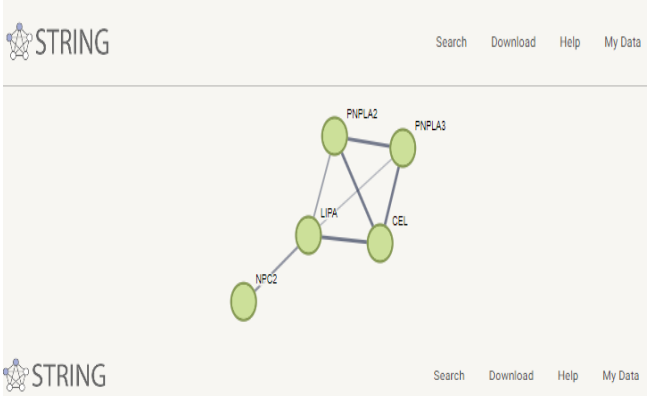
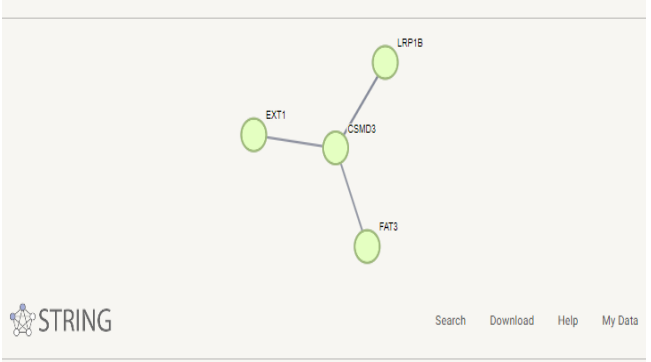
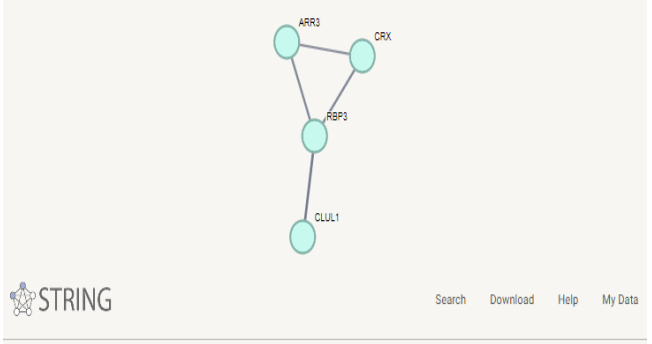
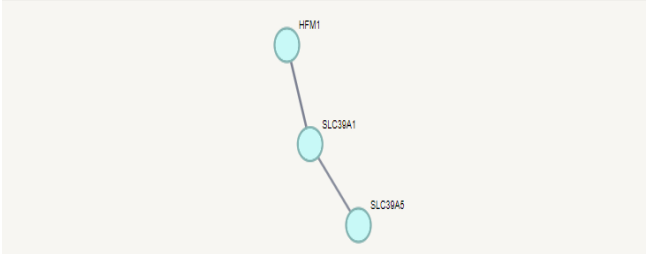
Sr. No.	Cluster No.	Cluster Structure
6	8	
7	9	
8	10	
9	11	
10	12	

Table 4.2: Cluster structures (Continued).

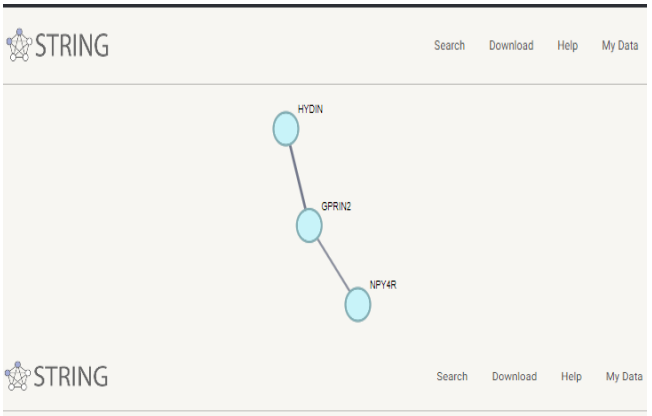
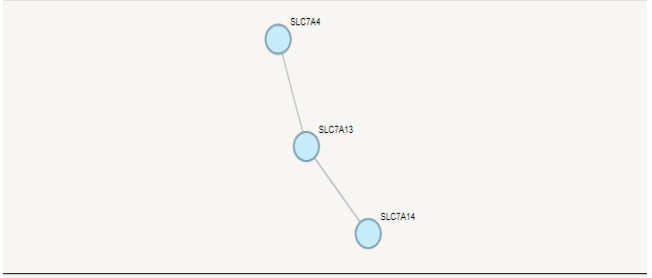
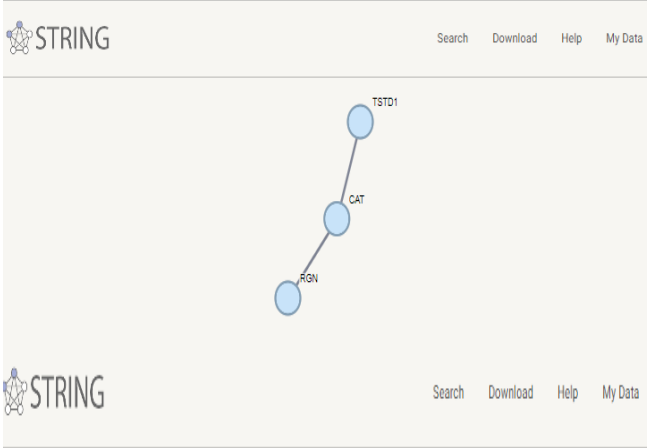
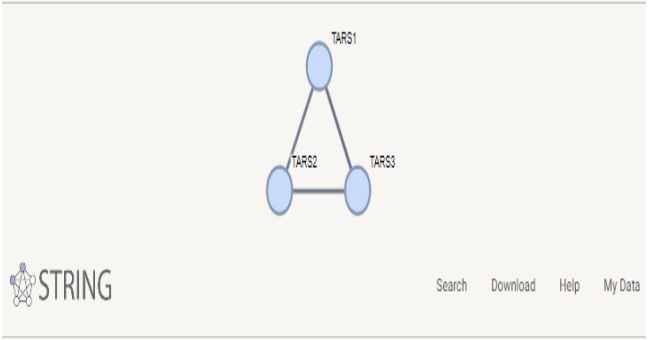
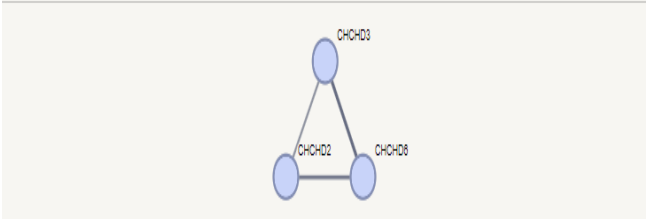
Sr. No.	Cluster No.	Cluster Structure
11	13	
12	14	
13	15	
14	16	
15	17	

Table 4.2: Cluster structures (Continued).

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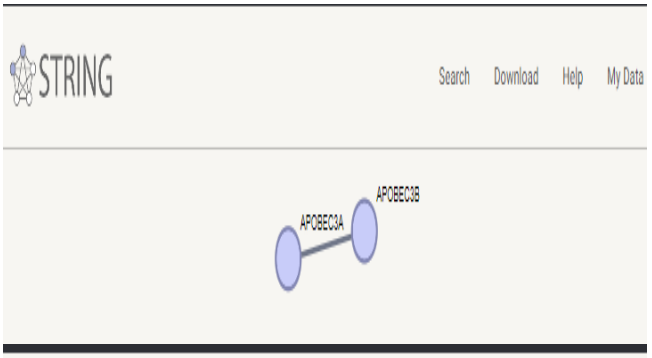
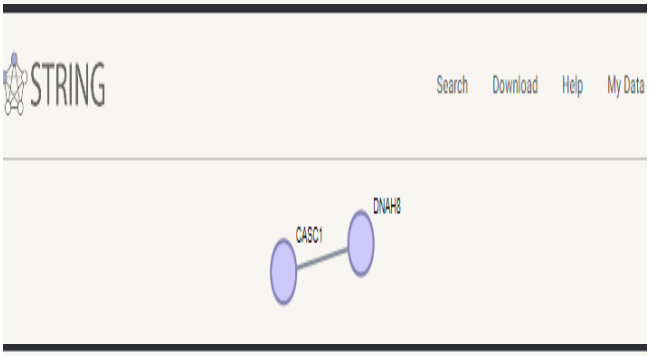
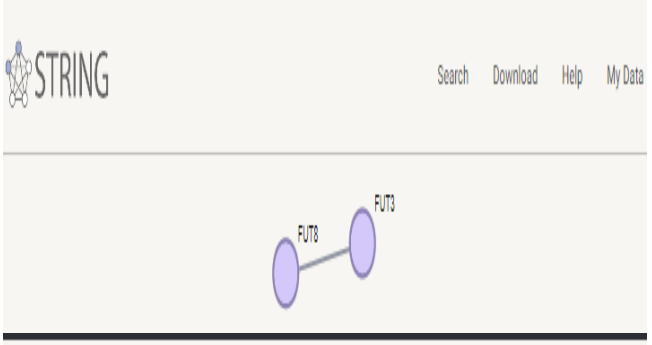
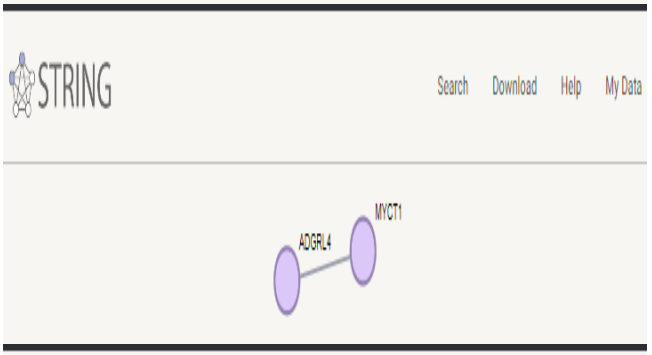
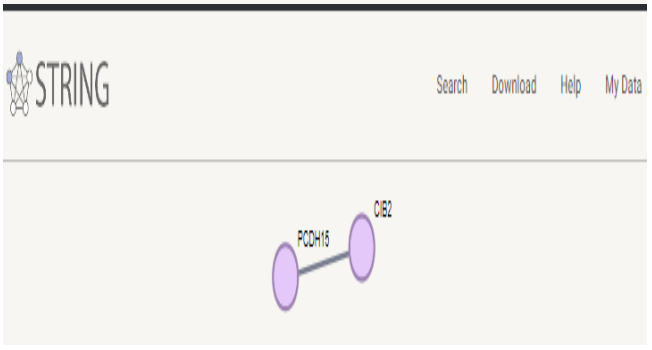
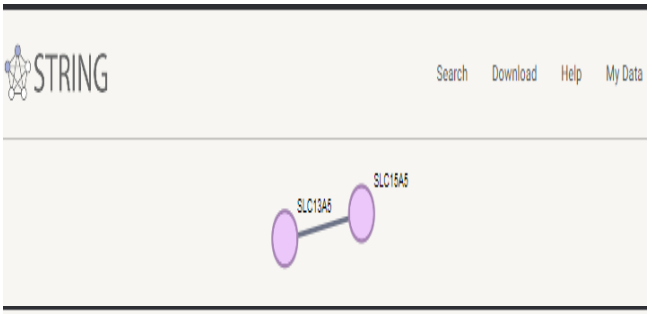
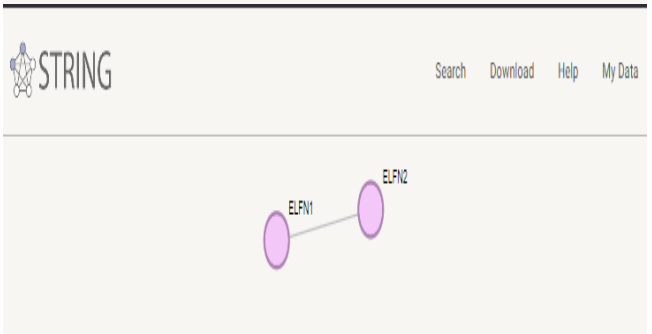
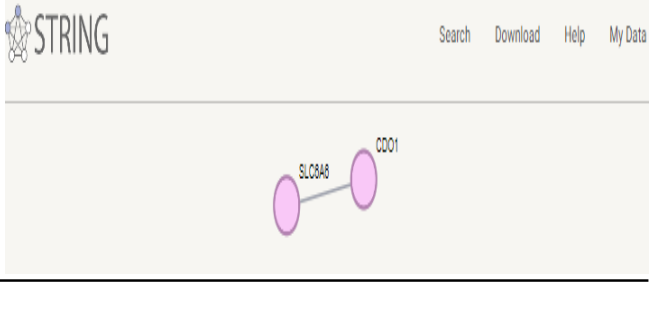
16	18	
17	19	
18	20	
19	21	
20	22	

Table 4.2: Cluster structures (Continued).

Sr. No.	Cluster No.	Cluster Structure
21	23	
22	24	
23	25	

4.4 Functional Annotation by DAVID Tool

Functional annotation was carried out using the David tool. Clusters were the outcome of the functional annotation process. We were able to create thirty distinct clusters for the retinoblastoma genes based on the output of the David tool.

4.4.1 Functional Annotation Clustering

4.4.1.1 Annotation Cluster 1

Annotation Cluster 1 has a 4.58 enrichment score in retinoblastoma gene functional annotation clustering. With an enrichment score of 4.58, genes related to foreign

substance transportation (p-value: 1.1E-5), the lowermost layer (p-value: 3.0E-5), and the lower side of plasma membranes (p-value: 5.9E-5) increased. This suggests certain biological processes and cellular components may cause retinoblastoma (Fig 4.3).

Annotation Cluster 1	Enrichment Score: 4.58		Count	P_Value	Benjamini
GOTERM_BP_DIRECT	xenobiotic transport	RT	5	1.1E-5	1.6E-3
GOTERM_CC_DIRECT	basal plasma membrane	RT	6	3.0E-5	1.5E-3
GOTERM_CC_DIRECT	basolateral plasma membrane	RT	9	5.9E-5	1.8E-3

FIGURE 4.3: Functional annotation clustering of retinoblastoma genes.

4.4.1.2 Annotation Cluster 2

Functional annotation clustering study of retinoblastoma genes showed 4.32 enrichment in Annotation Cluster 2. Many measures related to amino acid transport and transmembrane transporter activity increased in the study. Significant enrichment was seen for "amino acid transmembrane transporter activity" (p-value: 2.1E-8) and "Amino-acid transport" (2.6E-6). This suggests amino acid transport mechanisms may cause retinoblastoma (Fig 4.4)

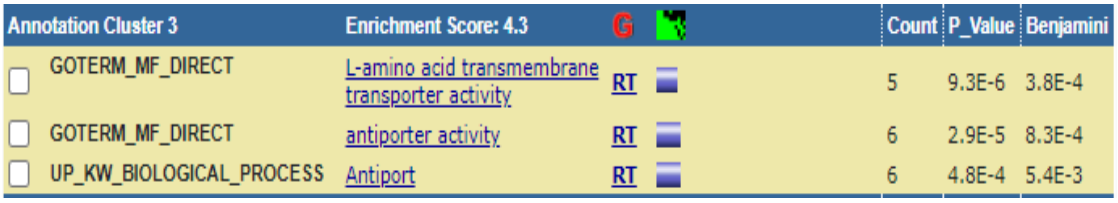
Annotation Cluster 2	Enrichment Score: 4.32		Count	P_Value	Benjamini
GOTERM_MF_DIRECT	amino acid transmembrane transporter activity	RT	7	2.1E-8	3.0E-6
UP_KW_BIOLOGICAL_PROCESS	Amino-acid transport	RT	7	2.6E-6	7.4E-5
GOTERM_BP_DIRECT	amino acid transport	RT	6	4.6E-6	9.6E-4
GOTERM_MF_DIRECT	L-amino acid transmembrane transporter activity	RT	5	9.3E-6	3.8E-4
INTERPRO	AA/rel permease1	RT	4	5.6E-5	3.8E-3
GOTERM_BP_DIRECT	neutral amino acid transport	RT	4	2.1E-4	1.6E-2
GOTERM_BP_DIRECT	amino acid transmembrane transport	RT	4	4.4E-4	2.8E-2
GOTERM_BP_DIRECT	leucine transport	RT	3	1.2E-3	5.5E-2
PIR_SUPERFAMILY	AA transporter	RT	3	1.6E-3	1.4E-2
GOTERM_MF_DIRECT	neutral amino acid transmembrane transporter activity	RT	3	2.9E-3	4.9E-2

FIGURE 4.4: Functional annotation clustering of retinoblastoma genes.

4.4.1.3 Annotation Cluster 3

Functional annotation cluster 3 of retinoblastoma genes has a 4.3 enrichment score. The study found significant increases in transmembrane transporter and antiporter

activities. The "L-amino acid transmembrane transporter" (p-value: 9.3E-6) and "antiporter" (p-value: 2.9E-5) activities were considerably enriched. Additionally, "Antiport" (p-value: 4.8E-4) was enriched. These data suggest that transmembrane transporter activity and antiporter activities may cause retinoblastoma (Fig 4.5).



Annotation Cluster 3	Enrichment Score: 4.3		Count	P_Value	Benjamini
GOTERM_MF_DIRECT	L-amino acid transmembrane transporter activity	RT	5	9.3E-6	3.8E-4
GOTERM_MF_DIRECT	antiporter activity	RT	6	2.9E-5	8.3E-4
UP_KW_BIOLOGICAL_PROCESS	Antiport	RT	6	4.8E-4	5.4E-3

FIGURE 4.5: Functional annotation clustering of retinoblastoma genes.

4.4.1.4 Annotation cluster 4

Functional annotation cluster 4 of retinoblastoma genes has an enrichment value of 4.26. Xenobiotic transporter activity and transmembrane helix properties increased significantly. Genes 1, 2, 3, and 8 with "TRANSMEM:Helical" features were significantly enriched (p-values 2.2E-3 to 5.3E-3). Additionally, "xenobiotic transporter activity" (p-value: 3.5E-9) was considerably elevated, suggesting that these activities may contribute to retinoblastoma (Fig 4.6).

4.4.1.5 Annotation cluster 5

Annotation Cluster 5, with a 3.92 enrichment value, substantially associates with ATPase, transmembrane transport, and xenobiotic transporter activity. Each of these factors helps transport molecules across membranes. The main findings include new words like xenobiotic transporter activity, ATPase-coupled transmembrane transporter activity, and drug transport routes. These pathways are important in retinoblastoma, suggesting ATPase activity and membrane transport treatment targets. The results from this cluster can help us understand the molecular pathways that cause retinoblastoma and its treatment resistance (Fig 4.7).

Annotation Cluster 4	Enrichment Score: 4.26	G		Count	P_Value	Benjamini
UP_SEQ_FEATURE	TRANSMEM:Helical; Name=8	RT		10	2.4E-9	1.7E-6
GOTERM_MF_DIRECT	xenobiotic transporter activity	RT		7	3.5E-9	1.0E-6
UP_SEQ_FEATURE	TRANSMEM:Helical; Name=12	RT		8	8.8E-8	3.1E-5
UP_SEQ_FEATURE	TRANSMEM:Helical; Name=11	RT		8	1.4E-7	3.3E-5
UP_SEQ_FEATURE	TRANSMEM:Helical; Name=10	RT		8	2.3E-7	4.1E-5
UP_SEQ_FEATURE	TRANSMEM:Helical; Name=9	RT		8	5.3E-7	7.5E-5
INTERPRO	MRP	RT		3	1.5E-4	6.0E-3
UP_SEQ_FEATURE	TRANSMEM:Helical; Name=16	RT		3	2.5E-4	1.2E-2
UP_SEQ_FEATURE	TRANSMEM:Helical; Name=17	RT		3	2.5E-4	1.2E-2
UP_SEQ_FEATURE	TRANSMEM:Helical; Name=15	RT		3	5.1E-4	2.0E-2
UP_SEQ_FEATURE	TRANSMEM:Helical; Name=14	RT		3	1.1E-3	3.6E-2
UP_SEQ_FEATURE	TRANSMEM:Helical; Name=3	RT		14	2.2E-3	6.7E-2
UP_SEQ_FEATURE	TRANSMEM:Helical; Name=4	RT		14	2.3E-3	6.7E-2
UP_SEQ_FEATURE	TRANSMEM:Helical; Name=13	RT		3	2.5E-3	7.0E-2
UP_SEQ_FEATURE	TRANSMEM:Helical; Name=1	RT		14	2.7E-3	7.0E-2
UP_SEQ_FEATURE	TRANSMEM:Helical; Name=2	RT		14	2.7E-3	7.0E-2
UP_SEQ_FEATURE	TRANSMEM:Helical; Name=6	RT		13	5.1E-3	1.1E-1
UP_SEQ_FEATURE	TRANSMEM:Helical; Name=5	RT		13	5.3E-3	1.1E-1
UP_SEQ_FEATURE	TRANSMEM:Helical; Name=7	RT		12	8.0E-3	1.6E-1

FIGURE 4.6: Functional annotation clustering of retinoblastoma genes.

Annotation Cluster 5	Enrichment Score: 3.92	G		Count	P_Value	Benjamini
GOTERM_MF_DIRECT	xenobiotic transporter activity	RT		7	3.5E-9	1.0E-6
GOTERM_BP_DIRECT	transmembrane transport	RT		12	5.3E-8	4.0E-5
GOTERM_MF_DIRECT	xenobiotic-transporting ATPase activity	RT		5	7.7E-7	5.5E-5
GOTERM_MF_DIRECT	ATPase activity, coupled to transmembrane movement of substances	RT		6	1.6E-6	9.1E-5
GOTERM_BP_DIRECT	leukotriene transport	RT		4	5.1E-6	9.6E-4
INTERPRO	ABC_transporter-like_ATP-bd	RT		6	6.1E-6	2.4E-3
GOTERM_MF_DIRECT	glutathione S-conjugate-exporting ATPase activity	RT		4	8.4E-6	3.8E-4
KEGG_PATHWAY	ABC transporters	RT		6	1.0E-5	8.9E-4
GOTERM_MF_DIRECT	ATPase-coupled anion transmembrane transporter activity	RT		4	1.8E-5	6.2E-4
UP_SEQ_FEATURE	DOMAIN:ABC transporter 1	RT		5	1.9E-5	1.9E-3
UP_SEQ_FEATURE	DOMAIN:ABC transporter 2	RT		5	1.9E-5	1.9E-3
KEGG_PATHWAY	Antifolate resistance	RT		5	4.1E-5	1.7E-3
SMART	AAA	RT		7	4.5E-5	1.1E-3
UP_SEQ_FEATURE	DOMAIN:ABC transmembrane type-1 1	RT		4	6.5E-5	4.6E-3
UP_SEQ_FEATURE	DOMAIN:ABC transmembrane type-1 2	RT		4	6.5E-5	4.6E-3
GOTERM_BP_DIRECT	drug transmembrane transport	RT		4	7.9E-5	7.1E-3
INTERPRO	AAA+_ATPase	RT		7	8.2E-5	3.8E-3
INTERPRO	ABC_transporter-like_CS	RT		5	8.8E-5	3.8E-3
UP_SEQ_FEATURE	DOMAIN:ABC transporter	RT		5	1.1E-4	6.5E-3
INTERPRO	MRP	RT		3	1.5E-4	6.0E-3
UP_SEQ_FEATURE	TRANSMEM:Helical; Name=16	RT		3	2.5E-4	1.2E-2
UP_SEQ_FEATURE	TRANSMEM:Helical; Name=17	RT		3	2.5E-4	1.2E-2
UP_KW_MOLECULAR_FUNCTION	Translocase	RT		6	3.1E-4	6.5E-3
GOTERM_BP_DIRECT	drug transport across blood-brain barrier	RT		3	4.2E-4	2.8E-2
INTERPRO	ABC1_TM_dom	RT		4	4.3E-4	1.3E-2
INTERPRO	ABC1_TM_sf	RT		4	4.3E-4	1.3E-2
GOTERM_BP_DIRECT	anion transmembrane transport	RT		4	4.9E-4	2.8E-2
UP_SEQ_FEATURE	TRANSMEM:Helical; Name=15	RT		3	5.1E-4	2.0E-2
GOTERM_MF_DIRECT	ATPase activity	RT		10	5.3E-4	1.0E-2
UP_SEQ_FEATURE	TRANSMEM:Helical; Name=14	RT		3	1.1E-3	3.6E-2
GOTERM_BP_DIRECT	transepithelial transport	RT		3	1.2E-3	5.5E-2
UP_SEQ_FEATURE	TRANSMEM:Helical; Name=13	RT		3	2.5E-3	7.0E-2
GOTERM_MF_DIRECT	efflux transmembrane transporter activity	RT		3	2.5E-3	4.5E-2
INTERPRO	P-loop_NTPase	RT		12	6.9E-3	1.1E-1
UP_SEQ_FEATURE	DOMAIN:ABC transmembrane type-1	RT		3	8.6E-3	1.6E-1
UP_KW_BIOLOGICAL_PROCESS	Lipid transport	RT		6	8.8E-3	5.5E-2
GOTERM_BP_DIRECT	bile acid and bile salt transport	RT		3	1.1E-2	3.0E-1
KEGG_PATHWAY	Bile secretion	RT		4	2.1E-2	2.0E-1
GOTERM_BP_DIRECT	xenobiotic metabolic process	RT		4	2.4E-2	4.9E-1

FIGURE 4.7: Functional annotation clustering of retinoblastoma genes.

4.4.1.6 Annotation Cluster 6

Annotation Cluster 6, with an enrichment value of 3.53, links retinoblastoma and retinitis pigmentosa visual perception systems. Visibility, photoreceptor cell outer segments, and retinitis pigmentosa are instances of heightened or detailed language. These findings suggest a relationship between photoreceptor function, vision, and retinal degenerative illnesses such retinitis pigmentosa and retinoblastoma. This cluster had less correlated sensory transduction pathways. These discoveries may help us understand how retinoblastoma affects visual circuitry and therapy options (Fig 4.8).

Annotation Cluster 6	Enrichment Score: 3.53			Count	P_Value	Benjamini
UP_KW_DISEASE	Retinitis pigmentosa	RT		9	4.7E-6	1.6E-4
GOTERM_BP_DIRECT	visual perception	RT		9	2.0E-5	2.5E-3
GOTERM_CC_DIRECT	photoreceptor outer segment	RT		6	2.6E-5	1.5E-3
UP_KW_BIOLOGICAL_PROCESS	Vision	RT		8	3.6E-5	6.8E-4
GOTERM_BP_DIRECT	photoreceptor cell maintenance	RT		4	2.0E-3	7.6E-2
GOTERM_BP_DIRECT	detection of light stimulus involved in visual perception	RT		3	6.1E-3	1.8E-1
UP_KW_BIOLOGICAL_PROCESS	Sensory transduction	RT		8	1.7E-1	4.8E-1

FIGURE 4.8: Functional annotation clustering of retinoblastoma genes.

4.4.1.7 Annotation Cluster 7

Annotation Cluster 7 focuses on retinoblastoma RNA processing pathways. Enrichment is 3.4 for this cluster. High concentration of "tRNA-splicing ligase complex" and "tRNA splicing via endonucleolytic cleavage and ligation" in Annotation Cluster 7. RNA processing pathways, especially tRNA splicing mechanisms, may cause retinoblastoma. A weaker association with RNA binding capacity is also shown by the cluster. These findings suggest that RNA processing disruption may cause retinoblastoma, stressing the need for further molecular research (Fig 4.9).

Annotation Cluster 7	Enrichment Score: 3.4			Count	P_Value	Benjamini
GOTERM_CC_DIRECT	tRNA-splicing ligase complex	RT		4	7.2E-6	1.1E-3
GOTERM_BP_DIRECT	tRNA splicing, via endonucleolytic cleavage and ligation	RT		4	3.2E-5	3.4E-3
GOTERM_MF_DIRECT	RNA binding	RT		11	2.7E-1	1.0E0

FIGURE 4.9: Functional annotation clustering of retinoblastoma genes.

4.4.1.8 Annotation Cluster 8

Based on retinoblastoma gene functional annotation grouping, Annotation Cluster 8 has a 2.99 enrichment score. Threonyl-tRNA aminoacylation, ligase activity, and tRNA binding are the main biological and molecular processes in this cluster. Protein domains and motifs involved in tRNA synthesis and editing are abundant in this cluster. ThrRS_core, Thr-tRNA-ligase_IIa, and TGS are examples. Interestingly, the P-values range from 7.7E-5 to 3.0E-1, indicating varying annotation relevance (Fig 4.10).

Annotation Cluster 8	Enrichment Score: 2.99	G		Count	P_Value	Benjamini
INTERPRO	ThrRS_core	RT		3	7.7E-5	3.8E-3
INTERPRO	Thr-tRNA-ligase_IIa	RT		3	7.7E-5	3.8E-3
INTERPRO	ThrRS_anticodon	RT		3	7.7E-5	3.8E-3
GOTERM_BP_DIRECT	threonyl-tRNA aminoacylation	RT		3	8.5E-5	7.1E-3
GOTERM_MF_DIRECT	threonine-tRNA ligase activity	RT		3	8.6E-5	2.3E-3
UP_KW_MOLECULAR_FUNCTION	Ligase	RT		7	2.7E-4	6.5E-3
SMART	tRNA_SAD	RT		3	4.4E-4	7.1E-3
UP_SEQ_FEATURE	DOMAIN:TGS	RT		3	5.1E-4	2.0E-2
INTERPRO	TGS	RT		3	5.3E-4	1.3E-2
INTERPRO	TGS-like	RT		3	5.3E-4	1.3E-2
INTERPRO	tRNA_SAD	RT		3	5.3E-4	1.3E-2
INTERPRO	Thr/Ala-tRNA-synth_IIc_edit	RT		3	7.1E-4	1.6E-2
INTERPRO	aa-tRNA-synt_IIb	RT		3	9.0E-4	1.9E-2
INTERPRO	Anticodon-bd	RT		3	9.0E-4	1.9E-2
INTERPRO	Anticodon-bd_dom_sf	RT		3	1.4E-3	2.5E-2
UP_SEQ_FEATURE	DOMAIN:Aminoacyl-transfer RNA synthetases class-II family profile	RT		3	2.2E-3	6.7E-2
INTERPRO	Beta-grasp_dom_sf	RT		3	2.6E-3	4.6E-2
INTERPRO	aa-tRNA-synth_II	RT		3	3.7E-3	6.0E-2
INTERPRO	aa-tRNA-synth_II/BPL/LPL	RT		3	8.3E-3	1.2E-1
UP_KW_MOLECULAR_FUNCTION	Aminoacyl-tRNA synthetase	RT		3	2.0E-2	2.8E-1
KEGG_PATHWAY	Aminoacyl-tRNA biosynthesis	RT		3	7.0E-2	3.8E-1
UP_KW_BIOLOGICAL_PROCESS	Protein biosynthesis	RT		3	3.0E-1	7.1E-1

FIGURE 4.10: Functional annotation clustering of retinoblastoma genes.

4.4.1.9 Annotation Cluster 9

Annotation Cluster 9 has an enrichment value of 2.7, indicating a significant increase in membrane-associated retinoblastoma gene functional annotations. Important annotations include N-linked glycosylation of asparagine residues, membrane location, and transmembrane helices. The words "membrane," "cell membrane," and "plasma membrane" strongly suggest cellular membrane components. Most annotations have low P-values, indicating statistical significance, however "Cell membrane" and "plasma membrane" have higher P-values, indicating lower importance than other phrases in the cluster (Fig 4.11).

Annotation Cluster 9	Enrichment Score: 2.7			Count	P_Value	Benjamini
UP_SEQ_FEATURE	CARBOHYD:N-linked (GlcNAc...) asparagine	RT		40	1.1E-4	6.5E-3
GOTERM_CC_DIRECT	membrane	RT		47	1.9E-4	4.7E-3
UP_SEQ_FEATURE	TOPO_DOM:Cytoplasmic	RT		36	2.0E-4	1.1E-2
UP_SEQ_FEATURE	TRANSMEM:Helical	RT		44	5.6E-4	2.0E-2
UP_SEQ_FEATURE	TOPO_DOM:Extracellular	RT		29	5.6E-4	2.0E-2
UP_KW_DOMAIN	Transmembrane helix	RT		50	6.2E-4	4.0E-3
UP_KW_DOMAIN	Transmembrane	RT		50	7.9E-4	4.0E-3
UP_KW_PTM	Glycoprotein	RT		42	2.9E-3	4.4E-2
UP_KW_CELLULAR_COMPONENT	Membrane	RT		57	5.4E-2	3.5E-1
UP_KW_CELLULAR_COMPONENT	Cell membrane	RT		29	1.4E-1	5.9E-1
GOTERM_CC_DIRECT	plasma membrane	RT		34	1.4E-1	8.3E-1

FIGURE 4.11: Functional annotation clustering of retinoblastoma genes.

4.4.1.10 Annotation Cluster 10

ATP binding and ATPase activity functional annotations in retinoblastoma genes are enriched in Annotation Cluster 10, with a 2.65 enrichment value. "ATPase activity" and "ATP binding" are strongly enriched in the cluster, and their low P-values indicate statistical significance. The high frequency of annotations for ATP-binding motifs and nucleotide-binding domains emphasizes the importance of ATP-related activities in retinoblastoma genes. While other sentences have moderately higher P-values, the enrichment emphasizes ATP-dependent pathways in retinoblastoma biology (Fig 4.12).

Annotation Cluster 10	Enrichment Score: 2.65			Count	P_Value	Benjamini
GOTERM_MF_DIRECT	ATPase activity	RT		10	5.3E-4	1.0E-2
GOTERM_MF_DIRECT	ATP binding	RT		20	5.3E-4	1.0E-2
UP_KW_LIGAND	ATP-binding	RT		20	4.0E-3	8.5E-2
INTERPRO	P-loop_NTPase	RT		12	6.9E-3	1.1E-1
UP_KW_LIGAND	Nucleotide-binding	RT		23	7.1E-3	8.5E-2

FIGURE 4.12: Functional annotation clustering of retinoblastoma genes.

4.4.1.11 Annotation Cluster 11

It has a 2.52 enrichment score, indicating that retinoblastoma genes have several functional annotations related to the TCA cycle. "Tricarboxylic acid cycle" and "citrate cycle (TCA cycle)" have low P-values, indicating high relevance. The high concentration of carbon metabolism annotations in this cluster emphasizes the importance of metabolic pathways in retinoblastoma biology. While certain phrases had higher P-values, the overall enrichment shows the importance of TCA cycle-related events in retinoblastoma gene activity (Fig 4.13).

Annotation Cluster 11	Enrichment Score: 2.52			Count	P_Value	Benjamini
GOTERM_BP_DIRECT	tricarboxylic acid cycle	RT		4	9.3E-4	5.0E-2
KEGG_PATHWAY	Citrate cycle (TCA cycle)	RT		4	9.7E-4	2.8E-2
KEGG_PATHWAY	Carbon metabolism	RT		5	6.8E-3	9.2E-2
UP_KW_BIOLOGICAL_PROCESS	Tricarboxylic acid cycle	RT		3	1.4E-2	7.8E-2

FIGURE 4.13: Functional annotation clustering of retinoblastoma genes.

4.4.1.12 Annotation Cluster 12

Annotation Cluster 12 has a 2.39 enrichment score, indicating that retinoblastoma genes have functional annotations related to ion transport, notably sodium transport. The terms "symporter activity" and "Symport" have low P-values, indicating high significance in this cluster. The presence of sodium ion and ion transport annotations suggests that sodium transport pathways may be involved in retinoblastoma biology. Although certain words had higher P-values, the overall enrichment shows the importance of ion transport-related activities in retinoblastoma gene activity (Fig 4.14).

Annotation Cluster 12	Enrichment Score: 2.39			Count	P_Value	Benjamini
GOTERM_MF_DIRECT	symporter activity	RT		6	1.9E-5	6.2E-4
UP_KW_BIOLOGICAL_PROCESS	Symport	RT		7	2.2E-4	3.1E-3
UP_KW_LIGAND	Sodium	RT		5	1.7E-2	1.3E-1
GOTERM_BP_DIRECT	sodium ion transmembrane transport	RT		4	2.4E-2	4.9E-1
UP_KW_BIOLOGICAL_PROCESS	Ion transport	RT		10	4.6E-2	2.0E-1
UP_KW_BIOLOGICAL_PROCESS	Sodium transport	RT		4	5.6E-2	2.1E-1

FIGURE 4.14: Functional annotation clustering of retinoblastoma genes.

4.4.1.13 Annotation Cluster 13

Functional annotations linked with retinoblastoma gene motifs and domains are enriched in Annotation Cluster 13, which has a 2.34 enrichment score. The phrases "Cx9C motif 1" and "Cx9C motif 2" have relevance in this cluster but poor P-values. The "CHCH" domain is also in this cluster, but its P-value is much greater. The annotations suggest that retinoblastoma biology may involve protein motifs and domains like the Cx9C motif and CHCH domain (Fig 4.15).

Annotation Cluster 13	Enrichment Score: 2.34			Count	P_Value	Benjamini
UP_SEQ_FEATURE	MOTIF:Cx9C motif 1	RT		3	4.0E-3	9.1E-2
UP_SEQ_FEATURE	MOTIF:Cx9C motif 2	RT		3	4.0E-3	9.1E-2
UP_SEQ_FEATURE	DOMAIN:CHCH	RT		3	5.9E-3	1.2E-1

FIGURE 4.15: Functional annotation clustering of retinoblastoma genes.

4.4.1.14 Annotation Cluster 14

It has a moderate enrichment of functional annotations related to lipid production in retinoblastoma genes (1.93). "Lipid biosynthesis" and "fatty acid biosynthetic process" have low to moderate P-values, indicating their relevance in this cluster. Fatty acid metabolism and mechanisms like AMPK activation are also annotated, with slightly larger P-values. Lipid biosynthesis pathways may play a moderate impact in retinoblastoma, according to annotations (Fig 4.16).

Annotation Cluster 14	Enrichment Score: 1.93	G		Count	P_Value	Benjamini
UP_KW_BIOLOGICAL_PROCESS	Lipid biosynthesis	RT		7	1.5E-3	1.4E-2
GOTERM_BP_DIRECT	fatty acid biosynthetic process	RT		4	2.7E-3	9.3E-2
UP_KW_BIOLOGICAL_PROCESS	Fatty acid biosynthesis	RT		4	6.6E-3	4.6E-2
UP_KW_BIOLOGICAL_PROCESS	Fatty acid metabolism	RT		5	3.1E-2	1.4E-1
KEGG_PATHWAY	AMPK signaling pathway	RT		4	4.5E-2	3.2E-1
KEGG_PATHWAY	Alcoholic liver disease	RT		4	6.7E-2	3.8E-1

FIGURE 4.16: Functional annotation clustering of retinoblastoma genes.

4.4.1.15 Annotation Cluster 15

Functional annotations related to eye development and transcriptional control in retinoblastoma genes are enriched in Annotation Cluster 15, with a score of 1.9. Names connected to homeobox domains, such as "HOX" and "Homeobox," have very low P-values, showing their importance in this cluster. Annotations on embryo skeletal system formation and anterior/posterior patterns emphasize developmental events in retinoblastoma biology. Although other words have higher P-values, the enrichment shows that transcriptional regulation and developmental pathways are important for retinoblastoma gene activity (Fig 4.17).

4.4.1.16 Annotation Cluster 16

Retinoblastoma genes were concentrated in pathways related to the nuclear pore complex and molecular transit between the nucleus and cytoplasm. An enrichment value of 1.8 shows strong annotation overrepresentation. The terms "structural constituent of nuclear pore" and "nuclear pore complex assembly" have low p-values. The pathways "Nucleocytoplasmic transport" and "mRNA transport" are also enriched, with P-values from 2.6E-3 to 5.4E-2 (Fig 4.18).

Annotation Cluster 15	Enrichment Score: 1.9			Count	P_Value	Benjamini
GOTERM_BP_DIRECT	eye development	RT		6	3.3E-6	9.6E-4
SMART	HOX	RT		9	1.9E-5	9.3E-4
UP_SEQ_FEATURE	DNA_BIND:Homeobox	RT		9	2.3E-5	2.1E-3
INTERPRO	Homeobox_dom	RT		9	5.3E-5	3.8E-3
INTERPRO	Homeobox_CS	RT		8	6.2E-5	3.8E-3
UP_KW_DOMAIN	Homeobox	RT		9	1.1E-4	1.6E-3
INTERPRO	Homeobox-like_sf	RT		9	2.7E-4	9.6E-3
UP_SEQ_FEATURE	DOMAIN:Homeobox	RT		6	5.0E-4	2.0E-2
INTERPRO	Homeobox_metazoa	RT		5	1.3E-3	2.5E-2
GOTERM_BP_DIRECT	embryonic skeletal system morphogenesis	RT		4	1.5E-3	6.1E-2
GOTERM_BP_DIRECT	anterior/posterior pattern specification	RT		5	1.6E-3	6.4E-2
UP_SEQ_FEATURE	DNA_BIND:Homeobox; TALE-type	RT		3	3.6E-3	8.7E-2
UP_SEQ_FEATURE	MOTIF:Antp-type hexapeptide	RT		3	5.9E-3	1.2E-1
INTERPRO	Homeobox_KN_domain	RT		3	8.3E-3	1.2E-1
GOTERM_BP_DIRECT	proximal/distal pattern formation	RT		3	8.5E-3	2.4E-1
GOTERM_MF_DIRECT	transcriptional activator activity, RNA polymerase II transcription regulatory region sequence-specific binding	RT		8	1.7E-2	2.4E-1
GOTERM_BP_DIRECT	animal organ morphogenesis	RT		4	2.3E-2	4.9E-1
KEGG_PATHWAY	Transcriptional misregulation in cancer	RT		5	3.8E-2	3.0E-1
UP_KW_MOLECULAR_FUNCTION	Developmental protein	RT		11	7.1E-2	5.9E-1
UP_KW_MOLECULAR_FUNCTION	Developmental protein	RT		11	7.1E-2	5.9E-1
GOTERM_MF_DIRECT	sequence-specific double-stranded DNA binding	RT		7	8.2E-2	5.2E-1
GOTERM_BP_DIRECT	positive regulation of transcription from RNA polymerase II promoter	RT		11	1.2E-1	1.0E0
GOTERM_CC_DIRECT	chromatin	RT		9	2.0E-1	9.7E-1
GOTERM_MF_DIRECT	transcription factor activity, sequence-specific DNA binding	RT		6	2.3E-1	1.0E0
GOTERM_MF_DIRECT	RNA polymerase II transcription factor activity, sequence-specific DNA binding	RT		10	2.4E-1	1.0E0
GOTERM_BP_DIRECT	brain development	RT		3	2.9E-1	1.0E0
GOTERM_CC_DIRECT	transcription factor complex	RT		3	3.2E-1	1.0E0
UP_KW_MOLECULAR_FUNCTION	Activator	RT		6	3.9E-1	1.0E0
GOTERM_MF_DIRECT	RNA polymerase II core promoter proximal region sequence-specific DNA binding	RT		8	4.5E-1	1.0E0
GOTERM_MF_DIRECT	DNA binding	RT		7	7.5E-1	1.0E0
UP_KW_MOLECULAR_FUNCTION	DNA-binding	RT		10	8.6E-1	1.0E0
GOTERM_BP_DIRECT	regulation of transcription from RNA polymerase II promoter	RT		7	8.7E-1	1.0E0
UP_KW_BIOLOGICAL_PROCESS	Transcription	RT		13	9.6E-1	1.0E0
UP_KW_BIOLOGICAL_PROCESS	Transcription regulation	RT		11	9.9E-1	1.0E0

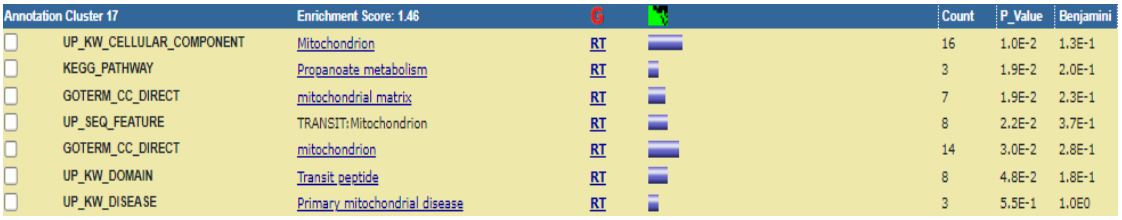
FIGURE 4.17: Functional annotation clustering of retinoblastoma genes.

Annotation Cluster 16	Enrichment Score: 1.8			Count	P_Value	Benjamini
GOTERM_MF_DIRECT	structural constituent of nuclear pore	RT		4	3.6E-4	8.7E-3
GOTERM_BP_DIRECT	nuclear pore complex assembly	RT		3	1.2E-3	5.5E-2
GOTERM_CC_DIRECT	nuclear pore	RT		5	1.6E-3	3.0E-2
GOTERM_BP_DIRECT	nucleocytoplasmic transport	RT		4	2.6E-3	9.2E-2
UP_KW_CELLULAR_COMPONENT	Nuclear pore complex	RT		4	2.9E-3	7.5E-2
GOTERM_CC_DIRECT	nuclear periphery	RT		3	3.4E-3	5.6E-2
KEGG_PATHWAY	Nucleocytoplasmic transport	RT		5	5.4E-3	9.2E-2
GOTERM_CC_DIRECT	nuclear envelope	RT		5	2.2E-2	2.5E-1
UP_KW_BIOLOGICAL_PROCESS	Translocation	RT		4	2.7E-2	1.4E-1
KEGG_PATHWAY	Amyotrophic lateral sclerosis	RT		7	3.2E-2	2.7E-1
UP_KW_BIOLOGICAL_PROCESS	mRNA transport	RT		4	5.4E-2	2.1E-1
GOTERM_BP_DIRECT	mRNA transport	RT		3	7.4E-2	9.0E-1
GOTERM_BP_DIRECT	protein import into nucleus	RT		3	1.0E-1	9.8E-1
GOTERM_CC_DIRECT	nuclear membrane	RT		4	1.5E-1	8.5E-1
GOTERM_BP_DIRECT	protein transport	RT		5	2.3E-1	1.0E0
UP_KW_BIOLOGICAL_PROCESS	Protein transport	RT		6	5.1E-1	1.0E0

FIGURE 4.18: Functional annotation clustering of retinoblastoma genes.

4.4.1.17 Annotation Cluster 17

With an enrichment score of 1.46, retinoblastoma gene functional annotation clustering shows a high concentration of mitochondrial genes. The terms "Mitochondrion" and "mitochondrial matrix" are enriched with p-values from 1.0E-2 to 3.0E-2. The mitochondrial function processes, such as "Propanoate metabolism," are also considerably enriched (P-value: 1.9E-2). However, annotations like "Primary mitochondrial disease" have a lower P-value (5.5E-1), indicating a possible association with lower confidence (Fig 4.19). Top of form



Annotation Cluster 17	Enrichment Score: 1.46			Count	P_Value	Benjamini
UP_KW_CELLULAR_COMPONENT	Mitochondrion	RT		16	1.0E-2	1.3E-1
KEGG_PATHWAY	Propanoate metabolism	RT		3	1.9E-2	2.0E-1
GOTERM_CC_DIRECT	mitochondrial matrix	RT		7	1.9E-2	2.3E-1
UP_SEQ_FEATURE	TRANSIT:Mitochondrion	RT		8	2.2E-2	3.7E-1
GOTERM_CC_DIRECT	mitochondrion	RT		14	3.0E-2	2.8E-1
UP_KW_DOMAIN	Transit peptide	RT		8	4.8E-2	1.8E-1
UP_KW_DISEASE	Primary mitochondrial disease	RT		3	5.5E-1	1.0E0

FIGURE 4.19: Functional annotation clustering of retinoblastoma genes.

4.4.1.18 Annotation Cluster 18

Clustering retinoblastoma genes shows a high conc. of annotations related to EGF-like domains and calcium ion binding, with an enrichment score of 1.2. "EGF-type-Asp/Asn-hydroxyl-site" and "EGF-Ca-bd-CS" have moderate significance (p-values of 1.7E-2 and 1.8E-2, respectively). Also enriched are EGF-like domain names "EGF-CA" and "EGF-like-Ca-bd-dom," with P-values from 2.5E-2 to 3.1E-2. However, the annotations "Calcium" and "Ca ion binding" had higher p-values (1.1E-1 to 4.1E-1), indicating less importance in this context (Fig 4.20).

Annotation Cluster 18	Enrichment Score: 1.2			Count	P_Value	Benjamini
INTERPRO	EGF-type_Asp/Asn_hydroxyl_site	RT		4	1.7E-2	2.1E-1
INTERPRO	EGF_Ca-bd_CS	RT		4	1.8E-2	2.1E-1
SMART	EGF_CA	RT		4	2.5E-2	3.0E-1
UP_SEQ_FEATURE	DOMAIN:EGF-like 1	RT		4	2.9E-2	4.6E-1
INTERPRO	EGF-like_Ca-bd_dom	RT		4	3.1E-2	3.0E-1
SMART	EGF	RT		4	6.7E-2	6.4E-1
UP_SEQ_FEATURE	DOMAIN:EGF-like 3	RT		3	6.8E-2	7.7E-1
UP_SEQ_FEATURE	DOMAIN:EGF-like	RT		4	1.0E-1	1.0E0
GOTERM_MF_DIRECT	calcium ion binding	RT		8	1.1E-1	6.4E-1
INTERPRO	EGF-like_dom	RT		4	1.4E-1	8.6E-1
UP_KW_DOMAIN	EGF-like domain	RT		4	1.8E-1	5.5E-1
UP_KW_LIGAND	Calcium	RT		9	4.1E-1	1.0E0

FIGURE 4.20: Functional annotation clustering of retinoblastoma genes.

4.4.1.19 Annotation Cluster 19

Peroxisome annotations increase significantly in functional annotation clustering analysis of retinoblastoma genes, with an enrichment score of 1.1. "Peroxisomal matrix" and "Peroxisome" are enriched with p-values of 2.8E-2 and 1.1E-1, respectively. The KEGG pathway "Peroxisome" also enriches, but with a higher p-value of 1.0E-1. Despite advances, peroxisome-related annotations seem rather important (Fig 4.21).

Annotation Cluster 19	Enrichment Score: 1.1	G		Count	P_Value	Benjamini
GOTERM_CC_DIRECT	peroxisomal matrix	RT		3	2.8E-2	2.8E-1
KEGG_PATHWAY	Peroxisome	RT		3	1.0E-1	4.9E-1
GOTERM_CC_DIRECT	peroxisome	RT		3	1.1E-1	7.2E-1
UP_KW_CELLULAR_COMPONENT	Peroxisome	RT		3	1.3E-1	5.9E-1

FIGURE 4.21: Functional annotation clustering of retinoblastoma genes.

4.4.1.20 Annotation Cluster 20

Functional annotation clustering of retinoblastoma genes has an enrichment value of 1.03, indicating a slight annotation overrepresentation. Cholesterol metabolism processes, such as "cholesterol metabolic process" and "Cholesterol metabolism," are enriched with p-values from 1.1E-2 to 8.9E-2. The annotations "Sterol metabolism" and "Steroid metabolism" also enrich, but with greater p-values of 1.1E-1 to 1.8E-1. The word "endoplasmic reticulum" also correlates, albeit with a p-value of 3.7E-1, suggesting less relevance in this context (Fig 4.22).

Annotation Cluster 20	Enrichment Score: 1.03	G		Count	P_Value	Benjamini
GOTERM_BP_DIRECT	cholesterol metabolic process	RT		4	1.1E-2	3.0E-1
UP_KW_BIOLOGICAL_PROCESS	Cholesterol metabolism	RT		3	8.9E-2	3.1E-1
UP_KW_BIOLOGICAL_PROCESS	Sterol metabolism	RT		3	1.1E-1	3.6E-1
UP_KW_BIOLOGICAL_PROCESS	Steroid metabolism	RT		3	1.8E-1	4.8E-1
GOTERM_CC_DIRECT	endoplasmic reticulum	RT		8	3.7E-1	1.0E0

FIGURE 4.22: Functional annotation clustering of retinoblastoma genes.

4.4.1.21 Annotation Cluster 21

Functional annotation clustering study of retinoblastoma genes shows a small annotation overrepresentation with an enrichment score of 1.02. Lipid metabolism

processes are highlighted, with "lipid homeostasis" having a considerable enrichment (P-value: 2.9E-2). Annotations like "lipid catabolic process" has a higher p-value (9.9E-2), indicating less statistical significance. The term "ACT-SITE:Nucleophile" suggests enzymatic involvement, however its importance is reduced by a p-value of 2.9E-1 (Fig 4.23).

Annotation Cluster 21	Enrichment Score: 1.02	G		Count	P_Value	Benjamini
GOTERM_BP_DIRECT	lipid homeostasis	RT		3	2.9E-2	5.4E-1
GOTERM_BP_DIRECT	lipid catabolic process	RT		3	9.9E-2	9.8E-1
UP_SEQ_FEATURE	ACT_SITE:Nucleophile	RT		4	2.9E-1	1.0E0

FIGURE 4.23: Functional annotation clustering of retinoblastoma genes.

4.4.1.22 Annotation Cluster 22

In functional annotation clustering analysis of retinoblastoma genes, an enrichment score of 0.92 indicates a minimal annotation representation issue. "DOMAIN:Cadherin" and related annotations are enriched. P-values range from 6.2E-2 to 1.1E-1, indicating modest statistical significance. However, phrases like "calcium ion binding" have a p-value of 1.1E-1, indicating less statistical significance. Additionally, cell adhesion mechanisms like "homophilic cell adhesion via plasma membrane adhesion molecules" and "Cell adhesion," have associations with p-values around 1.0, showing limited importance in this context (Fig 4.24).

Annotation Cluster 22	Enrichment Score: 0.92	G		Count	P_Value	Benjamini
UP_SEQ_FEATURE	DOMAIN:Cadherin	RT		3	6.2E-2	7.4E-1
UP_SEQ_FEATURE	DOMAIN:Cadherin 6	RT		3	6.4E-2	7.4E-1
UP_SEQ_FEATURE	DOMAIN:Cadherin 5	RT		3	9.6E-2	1.0E0
SMART	CA	RT		3	1.0E-1	8.2E-1
UP_SEQ_FEATURE	DOMAIN:Cadherin 3	RT		3	1.1E-1	1.0E0
UP_SEQ_FEATURE	DOMAIN:Cadherin 4	RT		3	1.1E-1	1.0E0
GOTERM_MF_DIRECT	calcium ion binding	RT		8	1.1E-1	6.4E-1
UP_SEQ_FEATURE	DOMAIN:Cadherin 1	RT		3	1.1E-1	1.0E0
UP_SEQ_FEATURE	DOMAIN:Cadherin 2	RT		3	1.1E-1	1.0E0
INTERPRO	Cadherin_CS	RT		3	1.1E-1	7.6E-1
INTERPRO	Cadherin-like_dom	RT		3	1.2E-1	7.9E-1
INTERPRO	Cadherin-like_sf	RT		3	1.3E-1	8.1E-1
GOTERM_BP_DIRECT	homophilic cell adhesion via plasma membrane adhesion molecules	RT		3	2.3E-1	1.0E0
UP_KW_BIOLOGICAL_PROCESS	Cell adhesion	RT		5	4.9E-1	1.0E0

FIGURE 4.24: Functional annotation clustering of retinoblastoma genes.

4.4.1.23 Annotation Cluster 23

In functional annotation clustering analysis of retinoblastoma genes, an enrichment score of 0.81 indicates a small annotation representation issue. Lipid metabolism

terms like "lipid droplet" and "lipid particle," with p-values of 5.4E-2 and 1.0E-1, respectively, show moderate significance. However, "ACT-SITE:Proton acceptor" has a higher p-value of 6.4E-1, indicating less importance. Although linked to lipid processes, this cluster is relatively unimportant (Fig 4.25).

Annotation Cluster 23	Enrichment Score: 0.81			Count	P_Value	Benjamini
UP_KW_CELLULAR_COMPONENT	Lipid droplet	RT		3	5.4E-2	3.5E-1
GOTERM_CC_DIRECT	lipid particle	RT		3	1.0E-1	6.9E-1
UP_SEQ_FEATURE	ACT_SITE:Proton acceptor	RT		5	6.4E-1	1.0E0

FIGURE 4.25: Functional annotation clustering of retinoblastoma genes.

4.4.1.24 Annotation Cluster 24

Functional annotation clustering study of retinoblastoma genes shows a substantial paucity of annotations with an enrichment score of 0.43. A p-value of 1.4E-1 indicates considerable importance for "protein glycosylation". However, annotations like "Golgi apparatus" and "Golgi membrane" have p-values near 1.0 (low relevance). Although less significant, "TOPO-DOM:Lumenal" and "TRANSMEM:Helical; Signal-anchor for type II membrane protein" also demonstrate connection with p-values of 2.5E-1 and 3.3E-1, respectively. This cluster lacks considerable retinoblastoma gene enrichment for these annotations (Fig 4.26).

Annotation Cluster 24	Enrichment Score: 0.5			Count	P_Value	Benjamini
UP_SEQ_FEATURE	REPEAT:4	RT		3	2.5E-1	1.0E0
UP_SEQ_FEATURE	REPEAT:3	RT		3	3.1E-1	1.0E0
UP_SEQ_FEATURE	REPEAT:1	RT		3	3.6E-1	1.0E0
UP_SEQ_FEATURE	REPEAT:2	RT		3	3.6E-1	1.0E0

FIGURE 4.26: Functional annotation clustering of retinoblastoma genes.

4.4.1.25 Annotation Cluster 25

In functional annotation clustering analysis of retinoblastoma genes, Cluster 25 has an enrichment value of 0.43, indicating a paucity of annotations. Golgi apparatus annotations include "protein glycosylation," "Golgi apparatus," and "Golgi membrane." These terms have high p-values, all near 1.0, suggesting they are unimportant in this context. Annotations like "TOPO-DOM:Lumenal" and "Signal-anchor" also correlate, but with p-values of 0.25 to 0.39, they are not statistically

significant. Overall, these annotations do not enrich retinoblastoma genes in this cluster (Fig 4.27).

Annotation Cluster 25	Enrichment Score: 0.43			Count	P_Value	Benjamini
GOTERM_BP_DIRECT	protein glycosylation	RT		3	1.4E-1	1.0E0
UP_SEQ_FEATURE	TOPO_DOM:Lumenal	RT		6	2.5E-1	1.0E0
UP_KW_DOMAIN	Signal-anchor	RT		5	2.8E-1	7.1E-1
UP_SEQ_FEATURE	TRANSMEM:Helical; Signal-anchor for type II membrane protein	RT		4	3.3E-1	1.0E0
UP_KW_MOLECULAR_FUNCTION	Glycosyltransferase	RT		3	3.9E-1	1.0E0
GOTERM_CC_DIRECT	Golgi apparatus	RT		7	4.9E-1	1.0E0
GOTERM_CC_DIRECT	Golgi membrane	RT		4	6.9E-1	1.0E0
UP_KW_CELLULAR_COMPONENT	Golgi apparatus	RT		4	9.3E-1	1.0E0

FIGURE 4.27: Functional annotation clustering of retinoblastoma genes.

4.4.1.26 Annotation Cluster 26

Annotation Cluster 26 has a low enrichment score of 0.42, indicating poor functional annotation enrichment in retinoblastoma genes. The data includes "LRR-TYP" and "Leu-ric-rpt," which are associated with LRRs. High P-values approaching 1.0 imply they are not statistically significant. Annotations for LRR repeats, such as "REPEAT:LRR 1" to "REPEAT:LRR 5," have substantial P-values, confirming this cluster's limited enrichment. Given the low enrichment score and huge P-values, LRR-related activities may not significantly affect retinoblastoma gene function (Fig 4.28).

Annotation Cluster 26	Enrichment Score: 0.42			Count	P_Value	Benjamini
SMART	LRR_TYP	RT		3	2.1E-1	1.0E0
INTERPRO	Leu-rich_rpt_typical-subtyp	RT		3	2.4E-1	1.0E0
UP_SEQ_FEATURE	REPEAT:LRR 5	RT		3	3.8E-1	1.0E0
UP_SEQ_FEATURE	REPEAT:LRR 4	RT		3	3.8E-1	1.0E0
INTERPRO	Leu-rich_rpt	RT		3	3.9E-1	1.0E0
UP_SEQ_FEATURE	REPEAT:LRR 3	RT		3	4.1E-1	1.0E0
UP_SEQ_FEATURE	REPEAT:LRR 2	RT		3	4.2E-1	1.0E0
UP_SEQ_FEATURE	REPEAT:LRR 1	RT		3	4.3E-1	1.0E0
INTERPRO	LRR_dom_sf	RT		3	5.2E-1	1.0E0
UP_KW_DOMAIN	Leucine-rich repeat	RT		3	5.5E-1	1.0E0

FIGURE 4.28: Functional annotation clustering of retinoblastoma genes.

4.4.1.27 Annotation Cluster 27

Annotation Cluster 27 has a low enrichment value of 0.4, indicating that functional annotations in retinoblastoma genes are only modestly enriched. The passage uses "defense response to virus" and "innate immune response." These terms have high P-values near 1.0, indicating no statistical significance. Although hydrolase

activity annotations have a moderately low P-value of 0.065, they are statistically more significant than immune-related keywords. Retinoblastoma gene function is not strongly associated with immunological response or antiviral defense, as seen by the low enrichment score and high P-values (Fig 4.29).

Annotation Cluster 27	Enrichment Score: 0.4	G		Count	P_Value	Benjamini
GOTERM_MF_DIRECT	hydrolase activity	RT		5	6.5E-2	4.6E-1
UP_KW_BIOLOGICAL_PROCESS	Antiviral defense	RT		3	2.6E-1	6.3E-1
GOTERM_BP_DIRECT	defense response to virus	RT		3	3.6E-1	1.0E0
GOTERM_BP_DIRECT	innate immune response	RT		3	7.8E-1	1.0E0
UP_KW_BIOLOGICAL_PROCESS	Innate immunity	RT		3	8.2E-1	1.0E0
UP_KW_BIOLOGICAL_PROCESS	Immunity	RT		3	9.9E-1	1.0E0

FIGURE 4.29: Functional annotation clustering of retinoblastoma genes.

4.4.1.28 Annotation Cluster 28

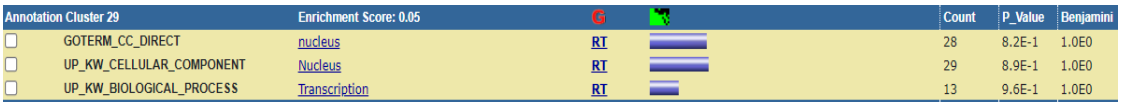
It has a low enrichment value of 0.09, indicating that retinoblastoma genes have few functional annotations. Although "metal ion binding" and "Metal-binding" are often used, their high P-values approaching 1.0 suggest no statistical relevance. More specifically, Mg and metal-binding annotations exhibited P-values of 0.57 and 1.0, respectively, indicating no enrichment. The low enrichment score and large P-values suggest that Mg and general metal-binding processes are unlikely to affect retinoblastoma gene activity (Fig 4.30).

Annotation Cluster 28	Enrichment Score: 0.09	G		Count	P_Value	Benjamini
UP_KW_LIGAND	Magnesium	RT		6	5.7E-1	1.0E0
GOTERM_MF_DIRECT	metal ion binding	RT		11	9.4E-1	1.0E0
UP_KW_LIGAND	Metal-binding	RT		16	1.0E0	1.0E0

FIGURE 4.30: Functional annotation clustering of retinoblastoma genes.

4.4.1.29 Annotation Cluster 29

Retinoblastoma genes have minor functional annotation enrichment in Cluster 29, which has a 0.05 enrichment score. The terms "nucleus" and "transcription," which refer to cellular localization and nucleus-related biological activities, are common. Even still, large P-values like 0.82 for "nucleus" and 0.96 for "Transcription," show no significant enrichment. As shown by the low enrichment score and high P-values, the retinoblastoma gene function may not be substantially associated to nuclear localization and transcriptional activity (Fig 4.31).



Annotation Cluster 29	Enrichment Score: 0.05			Count	P_Value	Benjamini
GOTERM_CC_DIRECT	nucleus	RT		28	8.2E-1	1.0E0
UP_KW_CELLULAR_COMPONENT	Nucleus	RT		29	8.9E-1	1.0E0
UP_KW_BIOLOGICAL_PROCESS	Transcription	RT		13	9.6E-1	1.0E0

FIGURE 4.31: Functional annotation clustering of retinoblastoma genes.

4.4.1.30 Annotation Cluster 30

Annotation Cluster 30 has a low enrichment value of 0.05, indicating few functional annotations in retinoblastoma genes. Includes "extracellular space" and "extracellular region," terms for outside cells. However, "extracellular space" (0.78) and "extracellular region" (0.94) have strong P-values, indicating no enrichment. Additionally, "Secreted" has a P-value of 0.99, indicating that it is not statistically significant. Data suggests that retinoblastoma gene function is not substantially connected to extracellular localization and secretion. The low enrichment score and huge P-values show this (Fig 4.32).

Annotation Cluster 30	Enrichment Score: 0.05			Count	P_Value	Benjamini
GOTERM_CC_DIRECT	extracellular space	RT		9	7.8E-1	1.0E0
GOTERM_CC_DIRECT	extracellular region	RT		8	9.4E-1	1.0E0
UP_KW_CELLULAR_COMPONENT	Secreted	RT		7	9.9E-1	1.0E0

FIGURE 4.32: Functional annotation clustering of retinoblastoma genes.

4.5 Cluster Validation Through Protein-Protein Interaction

Numbers of clusters were predicted using ProteinPrompt server. ProteinPrompt server is a tool that is connected to a database that provides connections of two nodes on experimental basis. For experimental validation of genes, ProteinPrompt server was utilized. The cluster containing genes *MEIS1, NUP62* and *CRX* were validated through experimental data present in ProteinPrompt server. In the realm of protein-protein interactions, a binding score is a quantitative measure that signifies the probability or intensity of the interaction between two proteins. The score normally spans from 0 to 1, with 1 denoting a flawless binding interaction, and lower scores indicating weaker or less likely interactions. The protein MEIS1 exhibits a binding score of 0.6200 (Fig 4.33). The binding score of 0.6200

suggests that there is a moderate probability or strength of binding interaction with the protein MEIS1. This score is significant because it allows researchers to determine the probability of protein interactions and their importance for further exploration. The score indicates that there is a significant likelihood of MEIS1 interacting with its binding partner, which is crucial for understanding its role in biological processes or disease mechanisms. The protein CRX has a binding score of 0.6667 (Fig 4.35). The score shows a strong and reliable interaction, implying a high likelihood that CRX has a meaningful interaction with its binding partner. This knowledge is essential for understanding the functional role of CRX in related biological pathways or disease processes. The protein NUP62 has a binding score of 0.6147 (Fig 4.34). This score indicates a moderate probability of contact. It indicates that NUP62 likely interacts with its binding partner but not as strong as that of CRX. This study provides vital insights into the likely functional importance of NUP62 in cellular activities. Results can be found under https://proteinformatics.uni-leipzig.de/ProteinPrompt/results/anonymous/aqelXWlx.

Protein	Score (1 = binding)	Uniprot ID
MEIS1	0.6200	O00470

FIGURE 4.33: Validated protein from cluster no 3.

Protein	Score (1 = binding)	Uniprot ID
NUP62	0.6147	P37198

FIGURE 4.34: Validated protein from cluster no 3.

Protein	Score (1 = binding)	Uniprot ID
CRX	0.6667	O43186

FIGURE 4.35: Validated protein from cluster no 11.

Chapter 5

Discussion

According to the available medical literature [1], retinoblastoma is a rare kind of cancer that mostly affects youngsters. This occurrence is documented. This disease manifests itself in the retina, which is the photosensitive tissue that covers the posterior portion of the eyeball and contains cells that have not yet reached their full maturity. The presence of retinoblastoma in babies can be observed from birth until about the age of five. Retinoblastoma subtype cancer accounts for around three percent of all instances of pediatric cancer that occur in children and adolescents under the age of fifteen [2].

Through the application of advanced biomedical text mining and bioinformatics techniques, the retinoblastoma mutations that we discovered were the primary focus of our research. Through the utilization of the MeSH database, we carried out an exhaustive investigation with the purpose of identifying genes that are especially associated with retinoblastoma. In order to ensure that we included the most recent and relevant scholarly works, the data gathering period for our study spanned a period of 10 years, beginning in 2014 and ending in 2024. The COREMINE Medical tool played a significant role in the extraction of a wide variety of biological entities from these texts. These entities included genes, proteins, MeSH names, processes, diseases, and drugs.

All of the information that was gathered was organized and analyzed in a thoughtful manner. A significant contribution was made by the KEGG pathway database

in the discovery of 38 pathways that are associated with retinoblastoma. With the use of the STRING database, we were able to locate gene clusters that ranged from three to twenty-five inside these pathways. This provides evidence that complex interaction networks are present, which may be involved in the development of retinoblastoma.

There were two pathways that were particularly significant: Pathway 4, which is connected with cancer, and Pathway 17, which is associated with Cushing syndrome. Both of these pathways are related to cancer. Cluster no. 4, which is associated with the *FH* gene, was highlighted by both groups of pathways. In addition, Cluster no. 20, which is connected to the *FUT8* gene, was highlighted in Pathway 34, which was primarily concerned with the transcriptional misregulation that occurs in cancer. Based on these findings, it is highly probable that *FH* and *FUT8* play significantly essential roles in the molecular pathways that are responsible for the development of retinoblastoma.

Utilizing DAVID tool, we conducted additional analysis to expand our list of predicted genes, with a special emphasis on those peculiar to *Homo sapiens*. We ensured that our findings are directly relevant and applicable to retinoblastoma in people by conducting an investigation that was limited to a certain species specifically. In the final stage of our investigation, we validated particular proteins from Cluster no. 3 and Cluster no. 11 by analyzing the interactions that these proteins have with other proteins. This was accomplished by utilizing the ProteinPrompt server, which was built by the University of Leipzig and utilized version 2.0. The validation approach has verified the interaction networks and functional significance of the identified proteins, thereby boosting the trustworthiness of our predictions.

The purpose of our research was to identify and validate new genetic variants that may be involved in the development of retinoblastoma. This was accomplished by efficiently combining a number of bioinformatics tools and approaches. Our understanding of the molecular basis of retinoblastoma has been improved as a result of these discoveries, which also have the potential to direct future research and treatment strategies.

Chapter 6

Conclusion and Future Prospects

6.1 Conclusion

The comprehensive investigation of genes associated with retinoblastoma through the application of a variety of bioinformatics techniques has resulted in the acquisition of significant knowledge regarding the molecular underpinnings of the disorder. Initially, the COREMINE tool was utilized in order to generate a substantial list of two thousand genes that are associated with retinoblastoma. The development of an interaction network consisting of 1870 nodes was made possible by additional investigation that made use of the STRING database. This network served as the basis for a more extensive functional study. The identification of gene clusters that are related with retinoblastoma was accomplished through the use of K-means clustering. Based on the findings of this investigation, significant biological pathways and processes that may have a role in the development of this disease were identified. These clusters were confirmed by the use of the KEGG pathway analysis, which found a total of 38 pathways that are connected with the illness. The use of the David tool for functional annotation clustering led to the discovery of thirty distinct groups, each of which provided essential clarification on a variety of biological processes and functions.

Annotation Cluster 1, which has a score of 4.58 for enrichment, has particularly identified genes that are associated with the movement of foreign substances and

components of the plasma membrane. A conclusion that can be drawn from this is that these activities might play a significant part in the development of retinoblastoma. Annotation Clusters 2 and 3 were discovered to be connected with activities related to amino acid transport and transmembrane transporter activities, respectively. This finding suggests that these clusters may play significant roles in the transmission of the disease. Additional clusters have been discovered, and they have been found to demonstrate significant activity connected with ATPase, xenobiotic transporters, and visual perception systems. We have a better understanding of retinoblastoma thanks to the unique contributions made by each of these clusters.

In addition, the verification of clusters accomplished through the utilization of the ProteinPrompt service brought to light the significance of protein-protein interactions in the process of appreciating the functional roles that particular genes play. The binding affinities of MEIS1, CRX, and NUP62 revealed large probabilities of interaction, which highlights the significance of these proteins in the processes that are linked with retinoblastoma.

Overall, bioinformatics research of retinoblastoma genes has laid a solid foundation for understanding the disease's molecular mechanisms. Following these criteria, future research may translate these findings into therapeutic applications, improving retinoblastoma outcomes.

6.2 Future Recommendations

1. To confirm their roles in retinoblastoma, genes and pathways should be empirically verified. In vitro and in vivo gene knockdown or over expression experiments in retinoblastoma cells can achieve this.

2. Functional studies on key genes in annotation clusters, such as amino acid transport, ATPase activity, and xenobiotic transporter activities, are needed. Understanding how these genes cause retinoblastoma can lead to new treatments.

3. To improve genomic data, proteomic analysis must identify retinoblastoma-related protein expression changes. This might help link genetic discoveries to disease-related protein levels and activities.

4. Expanding pathway analysis is needed to find medicinal targets in enriched pathways. Compounds that affect these targets should be tested in retinoblastoma models. Bioinformatics discoveries can be used with retinoblastoma patient data to confirm gene and pathway clinical importance. Personalized treatment strategies tailored to patients' genetic profiles may also result.

5. Longitudinal gene and protein expression investigations in retinoblastoma patients can reveal disease progression and therapy efficacy. These studies can uncover reliable biomarkers for retinoblastoma detection and tracking.

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