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A Study on Prevalence and Genetic Inheritance of Retinoblastoma

Susan George[1], R. Sangeetha*[2], V. Mohan Raj[3] and Jothilakshmi[4]

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A B S T R A C T

Retinoblastoma is a rare type of eye cancer that usually develops in early childhood, typically before the age of 5. This form of cancer develops in the retina, which is the specialized light-sensitive tissue at the back of the eye that detects light and colour. A study was carried out to find the influence of gender, age, consanguinity and genetic inheritance among Retinoblastoma patients whose history was collected from an eye hospital and results tabulated. Age and Gender showed an influence. The gender does not affect the prevalence as they are in their childhood. The disease Retinoblastoma recorded highest numbers between the age of 2 to 3 years of age and lowest number of patients were recorded above the age of 5 years. Female children were found to be affected more than the male children. Consanguinity was less noticed in the pedigree analysis of the Retinoblastoma patients. The patients of RB reported the highest genetic inheritance to be sporadic. A complete analysis was carried out from the patient's history collected for the study.

***Key words*:** Retinoblastoma, Eye, Pedigree analysis, Genetic Inheritance

The eye is a complex organ filled with many different parts that work together to produce clear vision. Eyes are approximately one inch in diameter. Pads of fat and the surrounding bones of the skull protect them. The eye has several major components: the cornea, pupil, lens, iris, retina, and sclera. This work together to capture an image and transmit it directly to the brain's occipital lobe via the optic nerve. When we look at an object, light reflected from it enters the eye and is refracted**,** or bent. This creates a focused, upside-down image of the object that the brain will have to interpret and turn in the correct direction. Inside the eye are photoreceptors**,** which create nerve impulses when struck by light. There are two types: cones make color vision possible, and rods specialize in black-and-white images. Our eyes can only see in two dimensions, called stereoscopic vision. A series of muscles helps the eye move. The first set is the superior and inferior rectus muscles, which allow upward and downward motion. The medial and lateral rectus muscles allow the eye to move from side to side while staying level. The superior and inferior oblique muscles let it move up or down and to the side. Most of these muscles are controlled by the oculomotor nerve.

Friction from these movements would quickly damage the eye without lubrication. Tears released by the lacrimal gland are spread around by blinking, and provide lubrication for the eye. Tears also help remove foreign objects and bacteria that could cause damage. Eye defects are a phenomenon many people deal with daily. In some cases, the defects of the eye are present from birth. Other types of eye defects are developed later in life. There are several eye conditions that are far more common than others. Fortunately, many of these common defects can be treated effectively. These are some of the eye diseases- Myopia, Hyperopia, Astigmatism, Glaucoma Cataract, Macular Edema, Cystoid Macular Edema, Drusen, keratonosus, macular degeneration, Leucoma, Leukoma, Retinopathy, Trachoma.

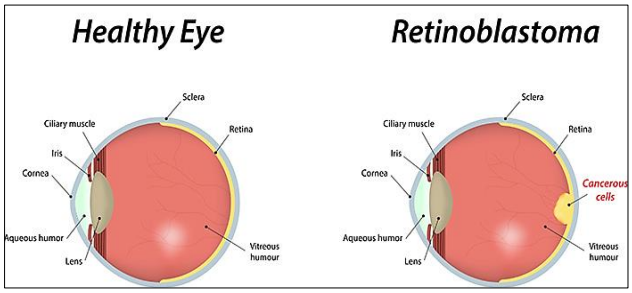
Retinoblastoma

Cancer starts when cells begin to grow out of control. Retinoblastoma is a cancer that starts in the retina, the very back part of the eye. It is the most common type of eye cancer in children. Retinoblastoma is often curable when it is diagnosed early. However, if it is not treated promptly, this cancer can spread beyond the eye to other parts of the body. This advanced form of retinoblastoma can be life-threatening.

When retinoblastoma is associated with a gene mutation that occurs in all of the body's cells, it is known as germinal retinoblastoma. People with this form of retinoblastoma also have an increased risk of developing several other cancers outside the eye. Specifically, they are more likely to develop a cancer of the pineal gland in the brain (pinealoma), a type of bone cancer known as osteosarcoma, cancers of soft tissues such as muscle, and an aggressive form of skin cancer called melanoma.

* **R. Sangeetha**
✉ drsangeethavijay@gmail.com

[1-4] P. G. & Research Department of Zoology, Sir Theagaraya College, Chennai - 600 021, Tamil Nadu, India

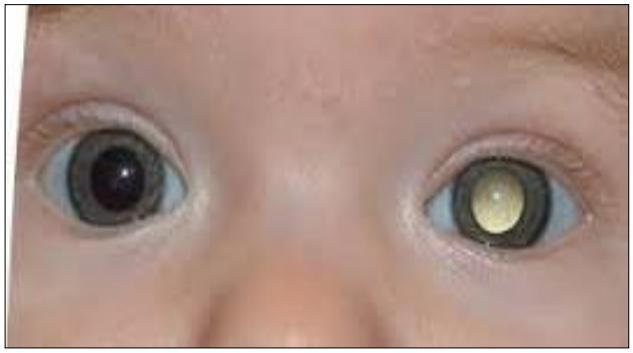


Source: https://www.aoa.org/healthy-eyes/eye-and-vision-conditions/retinoblastoma?sso=y

Development and growth of retinoblastoma

The eyes develop very early as babies grow in the womb. During the early stages of development, the eyes have cells called retinoblasts that divide into new cells and fill the retina. At a certain point, these cells stop dividing and develop into mature retinal cells. Rarely, something goes wrong with this process. Instead of maturing into special cells that detect light, some retinoblasts continue to divide and grow out of control, forming a cancer known as retinoblastoma.

The chain of events inside cells that leads to retinoblastoma is complex, but it almost always starts with a change (mutation) in a gene called the retinoblastoma (RB1) gene. The normal RB1 gene helps keep cells from growing out of control, but the change in the gene stops it from working like it should. Depending on when and where the change in the RB1 gene occurs, two different types of retinoblastoma can result. In most children with retinoblastoma, the disease affects only one eye. However, one out of three children with retinoblastoma develops cancer in both eyes. The most common first sign of retinoblastoma is a visible whiteness in the pupil called "cat's eye reflex" or leukocoria. This unusual whiteness is particularly noticeable in photographs taken with a flash. Other signs and symptoms of retinoblastoma include crossed eyes or eyes that do not point in the same direction (strabismus); persistent eye pain, redness, or irritation; and blindness or poor vision in the affected eye(s).



Retinoblastoma affected eye picture

If retinoblastoma tumours are not treated, they can grow and fill much of the eyeball. Cells might break away from the main tumour on the retina and float through the vitreous to reach other parts of the eye, where they can form more tumours. If these tumours block the channels that let fluid circulate within the eye, the pressure inside the eye can rise. This can cause glaucoma, which can lead to pain and loss of vision in the affected eye. Karina *et al*. [1] that the MIR-17-92 cleuter, is a potent micro-RNA encoding oncogene and its target of amplification and is highly expressed in retinoblastoma.

Most retinoblastomas are found and treated before they have spread outside the eyeball. But retinoblastoma cells can occasionally spread to other parts of the body. The cells sometimes grow along the optic nerve and reach the brain. Retinoblastoma cells can also grow through the covering layers of the eyeball and into the eye socket, eyelids, and nearby tissues. Once the cancer reaches tissues outside the eyeball, it can then spread to lymph nodes (small bean-shaped collections of immune system cells) and to other organs such as the liver, bones, and bone marrow (the soft, inner part of many bones).

Signs and symptoms of retinoblastoma

Retinoblastoma nearly always occurs in young children. They are often found when a parent or doctor notices a child's eye looks unusual. The most common sign are White pupillary reflex and Lazy eye. Less common signs and symptoms of retinoblastoma include Vision problems, Eye pain, Redness of the white part of the eye, Bleeding in the front part of the eye, Bulging of the eye, A pupil that doesn't get smaller when exposed to bright light, A different color in each iris (the colored part of the eye).

Incidence and key statistics

Retinoblastoma is a rare disease. Only about 200 to 300 children are diagnosed with retinoblastoma each year in the United States. It is more common in infants and very young children than in older children. The average age of children when they are diagnosed is 2. It rarely occurs in children older than 6. About 3 out of 4 children with retinoblastoma have a tumour in only one eye. In about 1 case in 4, both eyes are affected. Intraocular malignancy of infancy & childhood incidence 1/15,000-20,000 live birth [2].

Retinoblastoma is an ocular cancer that occurs most often in children under 5 years of age. Few known risk factors for retinoblastoma are age and heredity. Delayed metastasis in patients with intraocular retinoblastoma: A review of three cases is carried out by Vempuluru *et al*. [3]. Nikhil *et al*. [4] identified retinoblastoma binding protein 7 (Rbbp7) as a mediator against tau acetylation and subsequent neuronal loss in Alzheimer's disease and related tauopathies.

Genetic causes of retinoblastoma

Mutation of genes, found in chromosomes, can affect the way in which cells grow and develop within the body. Karina *et al*. [5] reported that Arf – critical tumor suppressed gene in deleted region. Inactivation of Arf cooperated with RB&P107 loss to rapidly accelerate RB. Alterations in RB1 or MYCN can give rise to retinoblastoma.

RB1

In children with the heritable genetic form of retinoblastoma there is a mutation in the RB1 gene on chromosome 13. RB1 was the first tumor suppressor gene cloned. Although RB1 interacts with over 100 cell proteins, its negative regulator effect on the cell cycle principally arises from binding and inactivation of the transcription factor E2F, thus repressing the transcription of

genes which are required for the S phase. The defective RB1 gene can be inherited from either parent; in some children, however, the mutation occurs in the early stages of foetal development. The expression of the RB1allele is autosomal dominant with 90% penetrance. RB is becoming increasingly complex ophthalmologists should be aware of other genomic changes in RB1 mutation [6]. Inherited forms of retinoblastomas are more likely to be bilateral. In addition, inherited uni or bilateral retinoblastomas may be associated with pineoblastoma and other malignant midline supratentorial primitive neuroectodermal tumours (PNET) with a dismal outcome; retinoblastoma concurrent with a PNET is known as trilateral retinoblastoma.

MYCN

Somatic amplification of the MYCN oncogene is responsible for some cases of non-hereditary, early-onset, aggressive, unilateral retinoblastoma. Although MYCN amplification accounted for only 1.4% of retinoblastoma cases, researchers identified it in 18% of infants diagnosed at less than 6 months of age. Median age at diagnosis for MYCN retinoblastoma was 4.5 months, compared with 24 months for those who had non-familial unilateral disease with two RB1 gene mutations.

Genetic inheritance of retinoblastoma

Researcher's estimate that 40 percent of all retinoblastomas are germinal, which means that *RB1*mutations occur in all of the body's cells, including reproductive cells (sperm or eggs). People with germinal retinoblastoma may have a family history of the disease, and they are at risk of passing on the mutated *RB1* gene to the next generation. The other 60 percent of retinoblastomas are non-germinal, which means that *RB1* mutations occur only in the eye and cannot be passed to the next generation.

In germinal retinoblastoma, mutations in the *RB1* gene appear to be inherited in an autosomal dominant pattern. Autosomal dominant inheritance suggests that one copy of the altered gene in each cell is sufficient to increase cancer risk. A person with germinal retinoblastoma may inherit an altered copy of the gene from one parent, or the altered gene may be the result of a new mutation that occurs in an egg or sperm cell or just after fertilization. In the non-germinal form of retinoblastoma, affected individuals are born with two normal copies of the *RB1* gene. Then, usually in early childhood, both copies of the *RB1* gene in retinal cells acquire mutations or are lost.

Congenital (hereditary) retinoblastoma

In about 1 out of 3 children with retinoblastoma, the abnormality in the RB1 gene is congenital (present at birth) and is in all the cells of the body, including all of the cells of both retinas. This is known as a germline mutation. Mortality increases in hereditary RB if irradiated [7]. In most of these children, there is no family history of this cancer. Only about 25% of the children born with this gene change inherit it from a parent. In about 75% of children the gene change first occurs during early development in the womb. The reasons for this are not clear. There is the risk of subsequent Malignant Neoplasms in Long-Terms Hereditary Retinoblastoma who have survived after chemotherapy and radiotherapy [8].

Children born with a mutation in the RB1 gene usually develop retinoblastoma in both eyes (known as bilateral retinoblastoma). Hereditary RB – constitutes a cancer pre disposition syndrome [9]. A small number of children with this form of retinoblastoma will develop another tumour in the brain, usually in the pineal gland at the base of the brain (a pineoblastoma). This is also known as trilateral retinoblastoma. Eye preservation survival ratio is high in bilateral-one eye enucleated patients [10]. Patricia *et al*. [11] studied the US unilateral sporadic tumour – rarely as bilateral hereditary and reported on maternal history of RB is found. Srividya *et al.* [12] reported that undetected RB leads to ocular mortality. Pre-natal diagnosis of RB and clinical follow up of strong family history of RB can prove efficient that if one child is affected at least other can be saved.

Sporadic (non-hereditary) retinoblastoma

In about 2 out of 3 children with retinoblastoma, the abnormality in the RB1 gene develops on its own in only one cell in one eye. It is not known what causes this change. A child who has sporadic (non-hereditary) retinoblastoma develops only one tumour in one eye. This type of retinoblastoma is often found at a later age than the hereditary form. Dong *et al.* [13] studied the genes of STAT 3 activated in RB cells of advanced stage. He also concluded that RB patients did not show positive staining of RB protein in tumour cells which is shown in normal retinal tissues.

Diagnosis and treatment

Hans *et al*. [14] studied the Genetic testing developed therapies in last 50 yrs and RB now be cured which was previously fatal. In diagnosis sometimes there are 40% chances of pseudo diagnosis of RB [15]. MRI role in diagnosing RB was proved necessary [16]. Pindegraaf *et al*. [17] studied the pretreatment diagnostic evaluation of RB and concluded MRI is the benefit for children worldwide, Shields *et al*. [18] carried out the chemotherapy alternatives intravenous, intra-arterial, periocular and intravitreal routes for bilateral RB.

Nicole *et al.* [19] studied the molecular Therapies and discussed for survival of children with tumour patients. Children thought to have retinoblastoma may have one or more of these tests-Ultrasound, Magnetic resonance imaging (MRI) scan, Computed tomography (CT) scan, Bone scan. The main types of treatment for retinoblastoma are Surgery, Radiation therapy (effective), Photocoagulation, Cryotherapy, thermotherapy, Chemotherapy, High-dose chemotherapy and stem cell transplant. Imaging techniques proves to be beneficial for diagnosis of RB [20], sometimes more than one type of treatment may be used. The treatment options are based on the extent of the cancer and other factors.

Thus, the aim of the study is Retinoblastoma an ocular cancer that occurs most often in children under 5 years of age. About 40% of all cases are inherited. Most children diagnosed with RB are younger than 3 years old. Most congenital or hereditary RB is found during the first year of life, while non-inherited RB tends to be diagnosed in 1-2 years old children. RB is rare in older children than in adults. The present study deals with children affected with RB along with consanguinity are considered to be the major factors in this study. The genetic inheritance of those affected children is drawn with a pedigree to prove their hereditary background. The consanguinity was also checked with the pedigree. The study is detailed on their inheritance of genes, a major factor in the development of generation.

MATERIALS AND METHODS

The method of study involves patients affected with RB. App. 30 patients with RB were selected for the study. A list from renowned eye hospital of RB patients was collected. These patients are questioned about their personal details such as

Name, Sex, Age, Place of Birth, Education, and Occupation Status. The Patients since they are young, the details are mostly acquired from their parents. The complete analysis of the patient from the age of onset of the disease till date is recorded. The family history with or without the diseased condition are discussed. A thorough analysis of the recorded details in the genetic clinical information sheet is tabulated.

RESULTS AND DISCUSSION

Patients visit the eye hospitals for various kinds of problems. The persons with a rare type of eye cancer that usually develops in early childhood, typically before the age of 5, termed retinoblastoma are isolated and a detail data was acquired from them or from their parents. All the data are collected and recorded in genetic clinical information sheet. The personal and genetic information's collected includes:

i) Patients name
ii) Patients sex
iii) Patients Age
iv) Place of Stay
v) Education & occupation details
vi) Conduct Number
vii) Age of onset of the condition.

A pedigree chart was drawn with the collected information's. Based on the pedigree analysis and the marriage background of the parents, the consanguinity is confirmed. Absence or presence of consanguinity also acts as an important factor in the present study.

Marriages among close relatives lead to consanguineous condition. Close relatives in a family tend to have related genetic makeup. So, it is taken as a factor for analysis in the present investigation and a cause for genetic inheritance. The genetic inheritance based on various tests was also recorded.

The genetical cause of retinoblastoma which are heritable are due to mutation in the RBI gene on chromosoma 13. The defective RBI gene can be inherited from either parent, in some children; however, the mutation occurs in the early stages of fetal development. The expression of the RBI allele is autosomal dominant with 90% penetrance. Inherited forms of retinoblastomas are more likely to bebilateral. Mutations in the RBI gene are responsible for most cases of retinoblastoma.

Nearly 30 patients affected with RB are selected and analyzed for various aspects. Among these patients 16 were females and 14 were males. The children since they are in their childhood are affected not based on gender. (Fig 1). All the details are tabulated together for comparison. The diagnosis of RB in children is successful with MRI. Children worldwide are benefited with MRI as pre-treatment diagnosis evaluation [17]. The patients of RB when compared with Age, the condition diagnosed at the age of 2. (Fig 2). The age can be taken as an important factor to analyze the disease. The children at the age of 2 to 3 years were accorded high with nearly 12 children. This constitutes 36% of the children concerned. Children of 4 to 5 years of age recorded 23% and children above five years of age recorded only 6% of the total children assessed. Children below 2 years and above 1 year were recorded to be 13%. Below 1 year the children with retinoblastoma condition recorded 16%. The disease showed the highest value between 4 to 5 years of age. The maximum patients with the disease record the highest within 1 to 5 years [21].

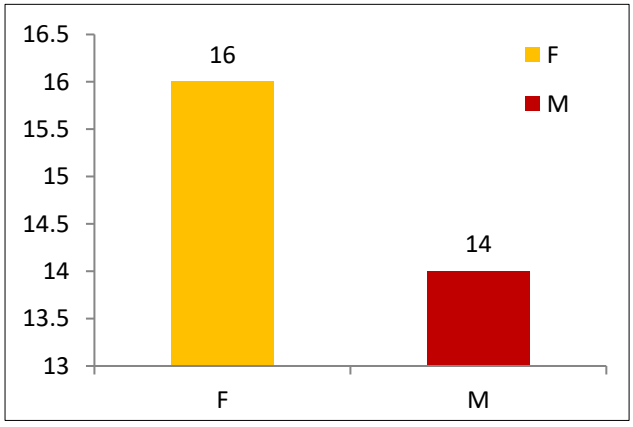


Fig 1 Number of RB patients vs gender

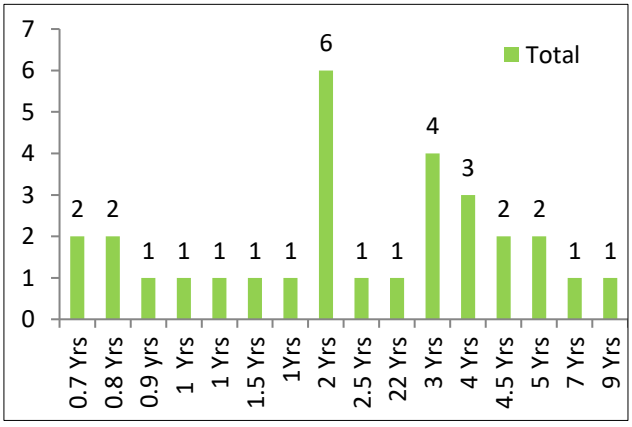


Fig 2 Number of RB patients vs age

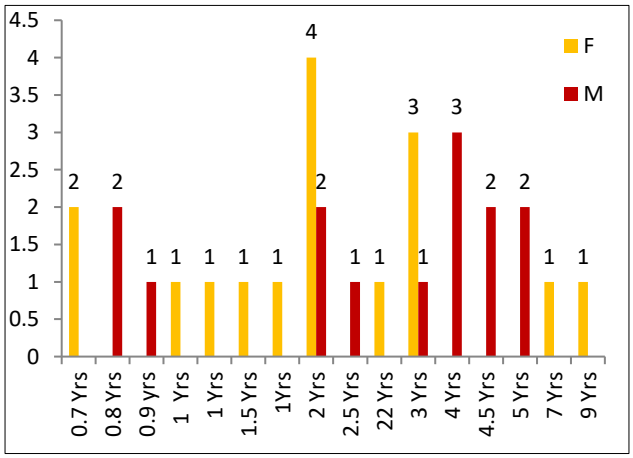


Fig 3 Number of RB patients vs age and gender

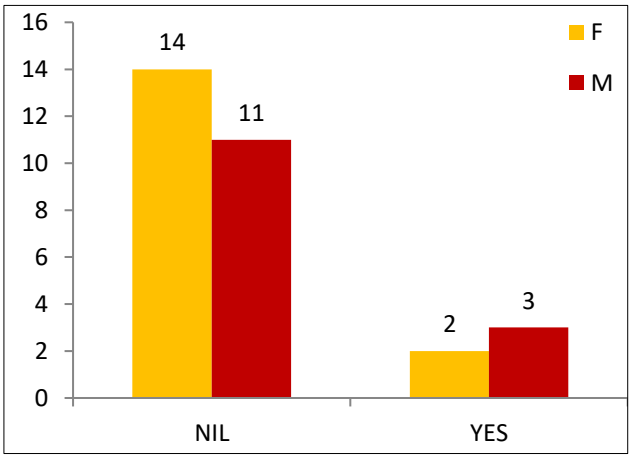


Fig 4 M&F RP patients vs consanguinity

Retinoblastoma patients when assessed based on Age and gender, below 1 year the males are affected more than female babies (Fig 3). Between one and two years of age, only females were recorded. Between 2 to 3 years which showed the maximum number of children also recorded the females higher than the male children. 4 to 5 years of children which recorded 23% were all males and children above 5 years who were diagnosed with RB were only females. Below the age of 5 which can be termed infancy and childhood the RB recorded 93%. This is in correlation with the results recorded as Intraocular malignancy always high during infancy and childhood [22].

Consanguinity, a condition of close relative's marriage sometimes causes diseases. It acts as one of the factors which increases the risk of incidence due to the double dose of the genes in these marriages. Analyzing retinoblastoma (RB) as one of these consanguineous diseases, the results recorded was not even 20 percent of the condition. Moreover, the males showed little higher incidence of consanguinity then female infants (Fig 4).

The patients of retinoblastoma (RB) while studying for genetic inheritance, the highest genetic cause were reported as sporadic. 22 patients out of 30 were affected with sporadic condition. 3 patients recorded autosomal Dominant condition (Fig 5) Unilateral condition and bilateral condition were one each. Sporadic is non-hereditary retinoblastoma develops only one tumor in one eye. This type of retinoblastoma is often found at a later age than the hereditary form. Unilateral sporadic turners are even found more in U.S [11]. Autosomal dominant inheritance suggests that one copy of the altered gene in each cell is sufficient to increase cancer risk. Dong Hyun Jo *et al*. [23] studied Antitumor Activity of Novel Signal Transducer and Activator of Transcription 3 Inhibitors on Retinoblastoma. Long-term risk of subsequent cancer incidence among hereditary and nonhereditary retinoblastoma survivors were noted by Sara *et al*. [24].

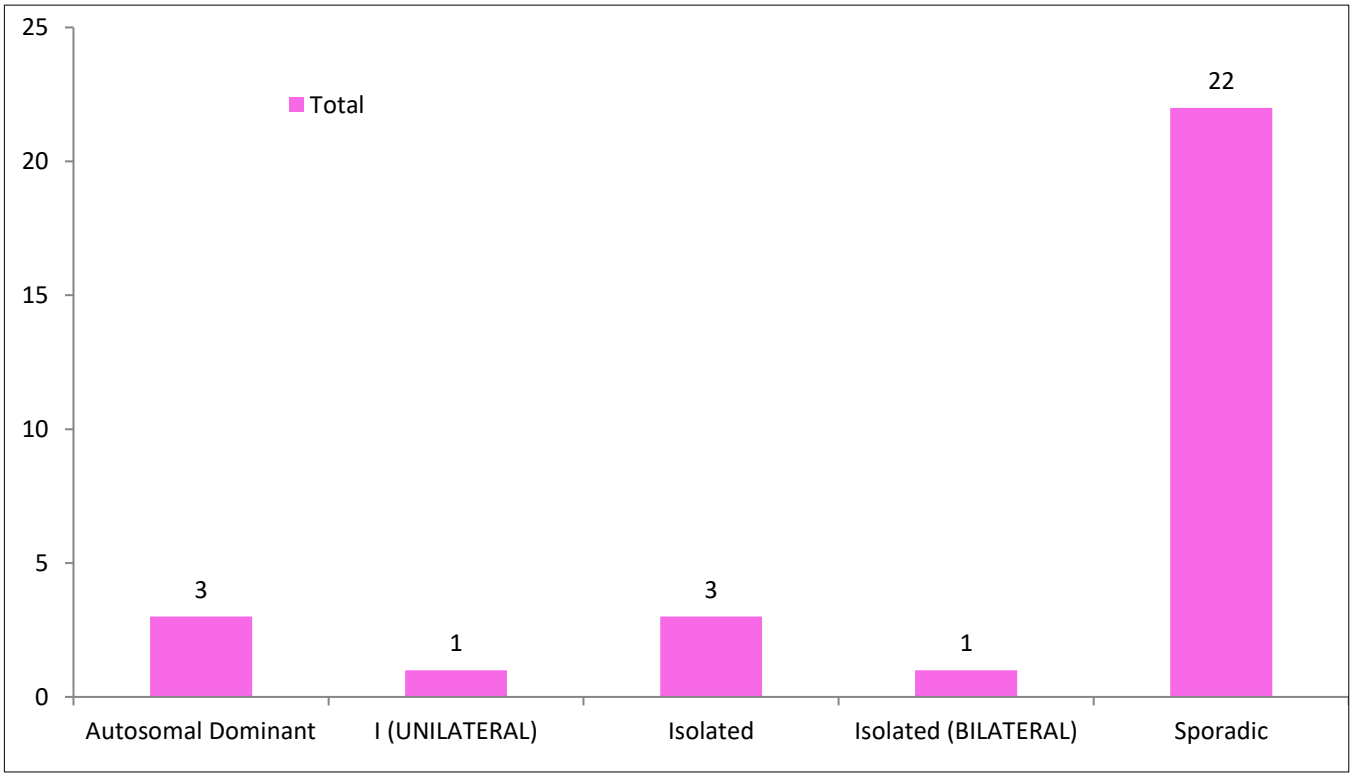


Fig 5 Retinoblastoma (RB) patients vs inheritance

Retinoblastomas nearly always occur in young children. The gender, age, consanguinity and genetic inheritance among young children were compared, thoroughly analyzed and discussed.

CONCLUSION

The patients with Retinoblastoma based on their age and severity of the disease they are at first placed for genetic counselling. Genetic counsellors are professionals who have completed a master's program in medical genetics and counselling skills. Genetic counsellors can help identify and interpret the risks of an inherited disorder, explain inheritance patterns, suggest testing, and lay out possible scenarios. Before collecting the family history information, the proband (person referred for genetic counselling) has to be informed about the pros and cons of the genetic counselling. This will help in getting detailed information for pedigree construction. Once the cancer is found and the needed tests have been done, the cancer care team will discuss treatment options with you. Most children with retinoblastoma are very young at the time of diagnosis. Still, some children may have emotional or psychological issues that need to be addressed during and after treatment. Depending on their age, they may also have some problems with normal functioning and school work. These can often be overcome with support and encouragement. Doctors and other members of the health care team can recommend special support programs and services to help children during and after treatment. Parents and other family members can also be affected, both emotionally and in other ways. The treatment center should evaluate the family situation as soon as possible. Some common family concerns include financial stresses, traveling to and staying near the cancer center, and the need for family members to take time off from work. If the patient or family members have concerns, they can be addressed before they become a crisis. Early intervention and counselling can also help address any psychological effects of changes in appearance.

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