Hereditary retinoblastoma

What is retinoblastoma?

Also called: RB

Retinoblastoma is an eye cancer that typically develops in children before 5 years of age. This cancer develops in the retina—the part of the eye that helps a person see color and light. Retinoblastoma may affect one or both eyes. In about two-thirds of all cases only one eye is affected.

Retinoblastoma is rare, with about 250–300 children diagnosed in the U.S. each year. The disease may be found during routine eye exams of young babies and toddlers. The child should then be referred to an eye specialist (ophthalmologist). Parents may notice one or more of the following:

- A white color to the pupil (the central portion of the eye that is usually black), especially with flash photography
- A misaligned or "lazy eye" (that may turn outward or inward when the child is looking straight ahead)
- Vision problems
- Red or irritated eyes

Most patients with retinoblastoma can be cured, especially if the disease is confined to the eyes. If left untreated, it can spread to other parts of the body, where it becomes much harder to treat.

What is hereditary retinoblastoma?

There are two types of retinoblastoma:

- Sporadic (not passed down in families)
- Hereditary (can be passed down in families)

Sixty percent of children have only one eye affected. Most of these children have the sporadic form of retinoblastoma. However, about 10%–15% may have hereditary retinoblastoma.

Forty percent of patients have both eyes affected. These children always have the hereditary form.

It is important to know whether a person has the hereditary or the sporadic form of retinoblastoma.

The hereditary form carries specific health risks that are not found with the sporadic form. Children with hereditary retinoblastoma are at an increased risk to:

- Develop other tumors (such as more retinoblastoma tumors, pineal gland tumors, skin, bone and muscle tumors)
- Develop second cancers after exposure to radiation.
- Transmit the condition to some of their future children

Children with sporadic retinoblastoma are not at risk to transmit the disease to their children. Their risk for developing second cancers is much less than the risk for children with hereditary retinoblastoma.

What causes hereditary retinoblastoma?

Hereditary retinoblastoma is caused by changes in a gene known as *RB1*. Genes carry important information that tells our body's cells how to function.

The *RB1* gene controls how cells grow and divide. One of its main jobs is to prevent tumors from forming, particularly retinoblastoma. Normally, your cells carry two working copies of *RB1*. One is inherited from your mother and one from your father.

Cells from people with hereditary retinoblastoma carry one working copy of *RB1* and one copy that is altered. This alteration causes the gene to not work properly and is called a mutation. When the remaining working copy of *RB1* becomes damaged within a cell of the developing retina, it is believed that this can lead to a retinoblastoma tumor. In about 10%–20% of hereditary retinoblastoma cases, this mutation is passed down from a parent who also has hereditary retinoblastoma. In the other cases, the affected child has a new mutation that was not present in either parent. While this child is the first one in the family to have hereditary retinoblastoma, he or she can now pass on the disease to 50% (1 in 2) of his or her future offspring.

What is the cancer risk for children with hereditary retinoblastoma?

Hereditary retinoblastoma might start in just one eye. But the chances of it developing in the second eye are high because cells in the other retina contain the altered *RB1* gene.

- Most children with hereditary retinoblastoma develop tumors affecting one or both of the eyes
- The risk to develop retinoblastoma tumors is greatest during the first five years of life
- A small number of children with hereditary retinoblastoma develop cancers outside the eyes, such as in the pineal gland of the brain. Later in life, tumors might form in other parts of the body (bones, muscle and skin).

How are children with hereditary retinoblastoma screened for cancer?

Children with hereditary retinoblastoma should be watched closely for the development of possible eye tumors. The goal is to detect cancer at the earliest and most treatable stage in order to minimize the therapy that is required and to preserve vision.

A specialized eye doctor called an ophthalmologist will conduct an eye exam as early as possible, even starting at birth, if there is a family history of retinoblastoma. Exams should then continue every one to two months during the first two years of life, and then less frequently as the child gets older. After age 5 years, regular yearly exams should occur for the rest of the patient's life. The ophthalmologist will decide how often the exams should take place.

Since there is also a small risk of tumors forming in the pineal gland, the child should have a magnetic resonance imaging (MRI) scan of the brain twice a year through age four years.

Currently, no standard exists for screening children with hereditary retinoblastoma for other (also called secondary) cancers. Families should watch for any signs or symptoms (lumps, bumps,

aches, pains, changes in moles or illness that does not go away) that cannot otherwise be easily explained. These should be evaluated by a health care provider, as they might be a sign of an underlying tumor. Patients should also see their regular health care provider at least yearly for a routine physical exam.

How do children get hereditary retinoblastoma?

In about 80%–90% of hereditary retinoblastoma cases, the child is the first person in the family to have the condition. In these cases, the *RB1* mutation either arose in an egg or sperm cell that formed the child or in one of the child's cells during pregnancy.

Less often, a child will develop hereditary retinoblastoma because the mother or father also carries the *RB1* mutation and passed it on to the child.

No matter how they acquired the altered gene, people with hereditary retinoblastoma have a 50% (or 1 in 2 chance) of passing it on to their children.

How is genetic testing for hereditary retinoblastoma done?

All children with both eyes affected and about 10%–15% of children with a single eye affected will have hereditary retinoblastoma. Genetic testing may be performed to find out whether a person has the hereditary or sporadic (non-hereditary) form of retinoblastoma.

Testing when eye tumor tissue can be used

- Retinoblastoma genetic testing is best performed by starting with a sample of the eye tumor. This can only be done if the entire eye is removed as part of disease treatment. A biopsy of the tumor is not performed due to the risk of spreading the disease outside the eye by removing tumor cells.
- DNA (genetic material) is isolated from a piece of the tumor
- The DNA is screened for any changes in the two copies of the *RB1* gene using methods such as DNA sequencing. In DNA sequencing, a genetic specialist checks the lettering (spelling) of the two copies of a gene to that of a normal sample. If there are differences, the specialist then decides if those differences might cause a disease, such as hereditary retinoblastoma. Please note that other methods may also be used, especially when the results of DNA sequencing are negative or unclear. These other tests look for changes that could affect the *RB1* gene but that may not be found by DNA sequencing.
- If the two *RB1* mutations that likely led to the formation of the retinoblastoma tumor are found, a separate blood sample from the person is checked for the presence of one of these mutations.
- Finding an *RB1* mutation in the blood supports a hereditary retinoblastoma diagnosis.
- The absence of an *RB1* mutation in the blood usually means that the child has sporadic retinoblastoma.

Testing when eye tumor tissue is not available

- *RB1* genetic testing can be performed on a blood sample from a child with retinoblastoma, even when there is no eye tumor available; however, it is sometimes harder to interpret the test results.
- If a disease-associated *RB1* mutation is found, the patient has hereditary retinoblastoma.
- If no *RB1* mutation is found, this does not rule out hereditary retinoblastoma. For example, it is possible that a mutation is present but it was not found because of limitations with the

testing process. Therefore, it is best to test the blood after the retinoblastoma-causing *RB1* mutations have first been found in the tumor.

RB1 genetic test results can provide important information for other family members. When a specific *RB1* mutation is found, other family members can be tested to see if they carry the same mutation.

Prenatal testing:
Parents may undergo prenatal testing to find out whether a pregnancy is affected with a known *RB1* mutation in the family.

Testing may take place either before pregnancy occurs or after an embryo is formed. Those considering prenatal testing should work with a genetic counselor to review the pros and cons of the tests. The genetic counselor will also help parents consider how they wish to handle the results of the testing.

Testing that occurs before pregnancy: Testing that happens before pregnancy is called preimplantation genetic testing (PGT). This special type of genetic testing is done along with in vitro fertilization (IVF). PGT offers a way to test embryos for a known *RB1* mutation before placing them into the uterus.

Testing that occurs during pregnancy: Testing can be used to determine if a pregnancy is affected with a known *RB1* mutation. A doctor gathers cells from the pregnancy in one of two ways:

- **Chorionic villus sampling (CVS)—**during first trimester
- **Amniocentesis—**during second trimester or later

Once these tissues are collected, DNA is isolated and checked for the presence of the *RB1* mutation identified in the family.

Both of these tests carry minor risks and should be discussed with an experienced doctor and/or genetic counselor.

Special concerns:
Genetic testing for hereditary retinoblastoma is a complex process. Those thinking about testing should take time to consider the benefits and risks. They should discuss the process with a genetic counselor before undergoing the testing. If they choose testing, they should review the test results with the health care provider or genetic counselor to be sure that they understand the meaning of the results.

Sometimes, children or adults with hereditary retinoblastoma experience sadness, anxiety or anger. Parents who passed on an altered *RB1* gene to one or more of their children can feel guilty. It is also possible that a person who is found to have an altered *RB1* gene could have more trouble getting disability insurance or life insurance.

Are there other special health care needs for children with hereditary retinoblastoma?

Survivors of hereditary retinoblastoma have a higher risk of other cancers later in life. It is recommended that they adopt healthy habits such as:

- Eat a healthy diet with lots of fruits and vegetables
- Get regular exercise
- Avoid excess sun exposure and always wear sunscreen, hat and protective clothing when out in the sun
- Avoid smoking or the use of tobacco products
- Avoid being around secondhand smoke
- Pay attention to unusual symptoms that could be signs of a tumor

As children with hereditary retinoblastoma grow up, they should continue to have regular physical checkups and screenings and maintain a primary pediatrician/physician. That way, any cancer can be found early at the most treatable stage.

People with hereditary retinoblastoma should also watch closely for symptoms that could signal cancer, such as:

- Unexplained weight loss
- Loss of appetite
- Aches, pains, lumps or swellings that cannot be explained
- Headaches or changes in vision or nerve function that do not go away
- New moles or changes in moles that are already present

Parents of children with hereditary retinoblastoma should seek medical help if these symptoms appear.

What other information and resources are there for children with hereditary retinoblastoma and their families?

Consult these resources to learn more about hereditary retinoblastoma:

- Retinoblastoma, American Cancer Society (http://www.cancer.org/cancer/retinoblastoma)
- Genetics Home Reference: (http://ghr.nlm.nih.gov/condition/retinoblastoma)
- National Organization for Rare Disorders: Retinoblastoma (*www.rarediseases.org/rare-disease-information/rare-diseases/byID/289/viewAbstract*)
- Young People with Cancer: A Parent's Guide (*www.cancer.gov/publications/patient-education/young-people*)
- Making Sense of Your Genes: A Guide to Genetic Counseling (*www.ncbi.nlm.nih.gov/books/NBK115508/*)

Sources:

1. American Cancer Society: Retinoblastoma
www.cancer.org/cancer/retinoblastoma/detailedguide/retinoblastoma-what-is-retinoblastoma
2. Genetics Home Reference: Retinoblastoma
ghr.nlm.nih.gov/condition/retinoblastoma
3. GeneReviews
www.ncbi.nlm.nih.gov/books/NBK1452/

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