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_RB1_ Mutations

Retinoblastomas (RB) occurs in two forms: hereditary and non-hereditary (sporadic). In hereditary retinoblastoma, a germline mutation in the *RB1* gene predisposes to the development of retinoblastoma. About 40% of retinoblastomas are hereditary, of which 80% arise from a *de novo* germline mutation (not inherited).[1]

Hereditary Retinoblastoma Risks

Hereditary Retinoblastoma: RB can be unilateral, bilateral, or trilateral (pinealoma).

- The majority of hereditary cases have bilateral or multifocal ocular involvement, but about 10-15% of children with unilateral, unifocal RB also have hereditary disease.[2]
- Bilateral RB typically presents earlier than unilateral RB, with a mean age of diagnosis of approximately 15 months compared with 24 months, respectively.[1]
- There is an approximately 2-5% risk of pineoblastoma among individuals with hereditary RB, with the lowest risk among those individuals that did not receive radiotherapy for intraocular disease.

Extra-Ocular Cancers: Individuals with a *RB1* gene mutation are at increased risk of developing second primary tumors. Most of the second primary cancers are osteosarcomas, soft tissue sarcomas, or melanomas. The risk of second primary tumors is about 20% in individuals with hereditary RB who have not received radiotherapy and substantially higher (40–50%) in those that have been irradiated.[1]

Hereditary Retinoblastoma Risk Management

Surveillance for intraocular RB[3]

Age	**Frequency**
Birth to 8 weeks	Non-sedated eye exams every 2-4 weeks
8 weeks to 12 months	Eye exam under anesthesia (EUA) monthly
12 to 24 months	EUA every 2 months
24 to 36 months	EUA every 3 months
36 to 48 months	EUA every 4 months
48 to 60 months	EUA every 6 months
5 to 7 years	Non-sedated eye exams every 6 months
7 years+	Non-sedated eye exams every 1-2 years

- RB treatment options include enucleation, cryotherapy, photocoagulation, photochemistry, external beam radiation therapy, and radiation therapy using episcleral plaques.
- Novel treatment options include systemic chemotherapy combined with or followed by local therapy using laser or freezing to physically destroy residual disease.

Surveillance for trilateral RB (pinealoma)

- Brain MRI is recommended at the time of diagnosis of RB, repeating every 6 months until 5 years of age[1]

Surveillance for second primary tumors[1]

- No established screening protocol
- Surveillance may include:
    - Annual physical exam, education regarding second primary tumor risks, and close attention to any new signs/symptoms. Individuals with bone pain, unusual lumps, bumps, or skin lesions should be promptly evaluated by their physicians.

- Skin exams performed by the pediatrician during well child visits, and continuing annually with the primary care physician or dermatologist from age 18 onward for melanoma
- Some groups consider whole body MRI annually after age 8, but there is currently no consensus

Agents to Avoid

- Individuals with retinoblastoma should avoid radiation when possible. They should also avoid exposure to UV light by wearing protective clothing and sunscreen and limiting outdoor activities. Individuals with retinoblastoma should avoid smoking and second hand smoke.

Implications for Family Members/Reproductive Considerations

- Approximately 80% of individuals with hereditary RB have a *de novo* mutation (not inherited from a parent). However, some individuals diagnosed with retinoblastoma have an affected parent or a parent who has an *RB1* gene mutation but is not affected. Therefore, we recommend testing parents for the known *RB1* gene mutation.
- Regardless of parental test results, testing siblings for the known *RB1* gene mutation can be considered. For all siblings that do not undergo genetic testing, eye examinations should be considered.
- Individuals with a *de novo RB1* mutation can still pass this on to their future children. Children have a 50% chance to have the mutation, if found in a parent.
- For carriers of a known mutation, assisted reproduction (with or without egg or sperm donation), pre-implantation genetic testing, and prenatal diagnosis options exist.
- All family members are encouraged to pursue genetic counseling to clarify their risks. Family members can visit www.FindAGeneticCounselor.com to find genetic services near them.

References

1. Kamihara J, Bourdeaut F, Foulkes WD, et al. Retinoblastoma and Neuroblastoma Predisposition and Surveillance. *Clinical cancer research : an official journal of the American Association for Cancer Research.* 2017;23(13):e98-e106.
2. Knudson AG, Jr. Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci U S A.* 1971;68(4):820-823.
3. Skalet AH, Gombos DS, Gallie BL, et al. Screening Children at Risk for Retinoblastoma: Consensus Report from the American Association of Ophthalmic Oncologists and Pathologists. *Ophthalmology.* 2018;125(3):453-458.