Retinoblastoma: Genetics That Affect Treatment and Lifelong Follow-Up

BY DENNY SMITH, CONTRIBUTING WRITER
INTERVIEWING DAVID H. ABRAMSON, MD, DANIELLE NOVETSKY FRIEDMAN, MD, BRENDA L. GALLIE, MD, AND LIVIA LUMBROSO-LE ROUIC, MD

A baby with a white pupil presenting to an ophthalmologist raises the familiar and often heartbreaking probability of retinoblastoma (RB). Leukocoria—sometimes with the additional signs of strabismus, ocular pain, and glaucoma—is the hallmark of the only childhood cancer that ophthalmologists are likely to encounter. Fortunately, the prognosis offered to traumatized parents has grown more optimistic in just a decade. There are now treatments—including intra-arterial chemotherapy—that can effectively cure the cancer and salvage affected eyes, while attentive follow-up ophthalmic care can preserve visual acuity in unaffected fellow eyes.

In fact, whether the child’s life, vision, and eyes are launched into healthy adulthood depends on the thoughtful attention of ophthalmologists—both the subspecialists who help parents make treatment decisions and the community ophthalmologists who follow retinoblastoma survivors for years. Many of the decisions that these physicians, the child’s parents, and, later, the child will face are grounded in the genetics of the disease.

Genetic vs. Heritable
RB is the prototypical “genetic cancer,” one which led to the recognition that all neoplastic processes arguably grow from cellular gene mutations. In 10-12 percent of families who have children with retinoblastoma, there is a history of the disease. The majority of these children are born into families with no history of retinoblastoma. A patient with the \( RB1 \) mutation in every cell of the body (“germinal”) has a 50 percent risk of each pregnancy giving rise to a child with retinoblastoma, either bilateral or unilateral, said David H. Abramson, MD, chief of the ophthalmic oncology service at Memorial Sloan Kettering Cancer Center.

Danielle Novetsky Friedman, MD, is a pediatrician at Memorial Sloan Kettering who specializes in treatment-related complications in childhood cancer survivors, particularly in RB survivors. Dr. Friedman said that oncogenesis of the nonheritable, or sporadic, form of RB is not well established. “For those without the hereditary form of disease, it is hard to say why retinoblastoma develops; this is also the case with the vast majority of pediatric cancers,” she said.

A recent study has shown that both copies of the \( RB1 \) gene are mutant in 97 percent of the nonheritable tumors. In 3 percent of nonheritable retinoblastoma, the \( RB1 \) gene is normal; and, instead, around 100 extra copies of the \( MYCN \) gene drive cancer development.\(^1\)

Even heritable RB does not always present with an extensive family history, Dr. Friedman said. But children with heritable RB are much more likely to have bilateral disease, which characterizes 40 percent of all cases; and those children are more likely to face secondary cancers in later life. Some patients actually have trilateral RB, with separate primary tumors arising in both eyes as well as in the pineal gland, the vestigial eye structure that persisted through evolution.

Uncharted genetic waters. Dr. Abramson said that another poorly understood wild card in genetic testing—mosaicism—is a limiting factor
for precise genetic diagnosis. “Perhaps 10 to 15 percent of retinoblastoma patients are genetically mosaic individuals. Mutations in this population are difficult, sometimes impossible, to detect with modern molecular analysis. This affects the precision of genetic testing and counseling. We really don’t know if mosaicism affects disease presentation or course/response to therapy, but recent work of ours suggests that the pattern of second tumors may be different in mosaics. Until we have long-term follow-up and concurrent molecular data, we cannot be sure.”

Brenda L. Gallie, MD, head of the retinoblastoma program at the University of Toronto, demonstrated that retinoblastoma can occur from mutations other than the RB gene. As complicated as all this information can be, Dr. Gallie points out that high-sensitivity technologies can identify 96 percent of RB1 gene mutations, enabling genetic counselors to advise RB families on their heritable status.

### Treatment: Genetics and Other Considerations

The question of sporadic or heritable RB is not merely academic, as the heritable form is more likely to cause bilateral disease, said Livia Lumbroso-Le Rouic, MD, at the Institut Curie in Paris. “Approximately 80 percent of unilateral retinoblastomas, and 50 percent of bilaterals, used to require enucleation of the eye. But these data have changed in recent years since the emergence of treatments that conserve the globe,” she said.

**Tx to save the eye.** The ratio of patients who had enucleations to those who survived with functional vision has dramatically improved thanks to the direct, arterial administration of therapeutic drugs into the eye, Dr. Abramson said. “As a result of intraarterial chemotherapy, enucleations are becoming rare in retinoblastoma. Overall, 90 percent of retinoblastoma survivors have 20/20 vision in at least one eye.”

**A case for enucleation.** But Dr. Gallie notes that trying to save an eye with RB represents challenges and investments that may seriously impair the quality of a child’s life. She noted that simple enucleation is highly likely to be curative, with the child back to full activity in 48 hours.

By comparison, she said, “attempted salvage of that unilateral RB eye would require several years of repeated treatments and monitoring under anesthetic—with recognized significant impact on learning and development. The eye is not more important than the whole child, whose life can be endangered if the tumor metastasizes during the effort to save an eye, or from the long, drawn-out, invasive therapy itself.

“Aggressive therapy may be well worthwhile in bilaterally affected children, to keep at least one eye, but may not be justified for children who have a normal eye. The choice to try to salvage an eye when the other eye will provide a lifetime of 20/20 vision needs careful weighing of all consequences,” she said.

### Living With Follow-Up

Even after treatment is completed in childhood, retinoblastoma patients and their physicians must be alert to numerous potential issues throughout their lives, from secondary cancers to family counseling. (See “Lifelong Health Concerns” for details.) Dr. Lumbroso-Le Rouic said the question of whether the RB is heritable or sporadic may determine how intensively the physician follows the patient or counsels the family.

**Secondary cancer risk.** “The long-term complications of retinoblastoma treatment are important but fortunately not common,” Dr. Abramson said. “In fact, they are probably less common or consequential than those faced by children who have survived other childhood cancers. We do know that the one important consequence of their gene mutation—a consequence sometimes amplified by their treatment—is cancer. The risk does not necessarily grow higher as they age; it may remain the same throughout life but never drops to zero.”

The question of how much risk for secondary cancers these patients face is complicated, Dr. Lumbroso-Le Rouic added. “Yes, if they carry the RB gene mutation, they are at higher risk for later cancers, and especially if they received radiation treatment. I can’t say with certainty whether the risk decreases or increases with age, but I personally have seen several patients developing osteosarcomas very late in life.”

Essentially, Dr. Abramson said, “Retinoblastoma patients who have the heritable form of the disease are at lifelong risk for the development of cancer. Data on the expectations of the timing, type, and incidence of these second cancers are available at [retinoblastoma.com](http://www.retinoblastoma.com). External beam radiation, especially in the first year of the child’s life, increases this risk manyfold, as does exposure to systemic chemotherapy.”

Long-term follow-up for cancer detection and recommendations for screening are usually handled by ocu-
Ocular and Pathology

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takes place Saturday, Oct. 18, from 8 a.m. to 5:15 p.m. Plan to attend!

Program directors Hans E. Grossniklaus, MD, and Arun D. Singh, MD, are working to develop an exciting and informative meeting that, among other topics, will include discussion of retinoblastoma—from clinical aspects, pathology, and genetics to therapies ranging from intra-arterial chemotherapy, intravitreal injections, gene therapy, and nanoparticle therapy.

In conjunction with the American Association of Ophthalmic Oncologists and Pathologists.