



Retinoblastoma Solutions

Molecular Diagnostic Laboratory

May, 2006

Background for Retinoblastoma Families and Those who Provide Care

About Us

Retinoblastoma Solutions is a global reference lab and a non-profit charity. We provide analysis for all retinoblastoma families, whether unilaterally and bilaterally affected, and whether or not retinoblastoma tumor tissue is available for analysis. We also offer pre-natal testing from either a sample of chorionic villi or cultured amniotic cells.

Retinoblastoma Solutions analyzes a relatively large volume of specimens (over 100 new families each year) referred by specialists from many countries. Our methods are optimized to provide the most powerful genetic analysis for retinoblastoma families worldwide at the lowest sustainable cost, with rapid turnaround time and minimum chance of errors.

Please tell others about us! We are glad for each opportunity to help retinoblastoma families and higher volumes mean lower costs for each family. Please pass this sheet along to your doctors, genetic counselors, and others who might benefit.

Performance Measures: Sensitivity, Specificity and Turnaround Time

For 649 different families (as of May 2006), our lab completely diagnosed 321 of 346 (92.8 %) bilateral probands, 257 of 283 (90.8 %) tumors from unilateral probands with no known family history, and 18 of 20 (90 %) unilateral probands with prior family history of retinoblastoma. Whenever possible, Retinoblastoma Solutions banks DNA and RNA for tests not yet invented.

Outside of human error, identification of genetic mutations is 100% specific.

Average turnaround time to identify a family's unknown mutation is 5.5 weeks. Diagnosis takes between 4 and 5 weeks for most families, but for a minority, an exhaustive search or additional analysis stretches turnaround time to as long as 12 weeks.

Our Mutation Identification Strategy

For unilateral patients with no family history of retinoblastoma, it is ideal to obtain DNA from both a fresh or frozen tumor sample and a blood sample. Useful limited analysis is feasible, however, for unilateral individuals whose tumor is no longer available in useful form. For bilateral patients, we require DNA from a blood sample only. Our test protocol is a series of molecular tests on DNA performed in the order that maximizes efficiency in finding mutations. To analyze a family's DNA, our laboratory:

- sequences the 27 exons and the promoter region of the *RB1* gene.
- uses quantitative multiplex PCR to detect deletions, duplications or insertions in the 27 exons and the promoter region, and to measure exon copy number.
- checks the sequence of abnormally sized fragments using an automated sequencer and stops sequencing if biologically likely (causative) mutations are found.
- performs promoter-targeted methylation-specific PCR on tumor for unilateral patients with no apparent family history.
- analyzes transcription function for suspect splice-site mutations.

Retinoblastoma Solutions does not offer linkage analysis at this time.

About Retinoblastoma Genetics

Retinoblastoma is the most common childhood intraocular cancer. Retinoblastoma tumors grow either because both the paternal and maternal copies of the *RB1* gene in a cell are mutated or because one copy is mutated and the second copy is lost (loss of heterozygosity). Non-heritable retinoblastoma arises when two mutations occur after cell differentiation, usually in retinal cells. Most patients show tumor symptoms before the age of three years.

Positive family history accounts for only 10% of retinoblastoma cases. Heritable retinoblastoma arises in most cases due to a new germline mutation and not due to a mutation inherited from a parent. Probands affected with heritable retinoblastoma have a 50% chance of passing this mutation to their children. In most families, a person who inherits an *RB1* gene mutation is predisposed to develop retinal tumors (95% risk).

The majority of heritable cases are identified by the occurrence of bilateral tumors. Non-heritable retinoblastoma is always unilateral, but 15% of children clinically identified with unilateral tumors actually have heritable retinoblastoma. Heritable retinoblastoma in a unilateral patient can be distinguished from non-heritable, somatic cell retinoblastoma only by searching DNA from the patient's blood for all mutations identified in the patient's tumor tissue.

Successful identification of a causative mutation can determine whether a proband has heritable or non-heritable retinoblastoma and which family members are at risk for tumor development. The *RB1* test protocol characterizes a mutation in 92% of affected patients. Once an *RB1* gene mutation is detected in an affected proband, molecular analysis of relatives at risk can identify those family members who have no need of examinations under anesthetic (approximately 90%) and those who carry the mutation and who should be offered frequent clinical screening (approximately 10%). Early detection preserves the vision and eyes of children, because most small tumors can be treated successfully.

Questions Welcome

We exist to serve retinoblastoma families and we welcome questions about retinoblastoma, genetics, and genetic testing. Please feel free to contact us!

Contact Information

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