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Clinical Use of Molecular Genetic Studies in Retinoblastoma

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With a population incidence of about 1 in 15.000 retinoblastoma is the most frequent intraocular tumor in infancy and early childhood. It occurs in a hereditary form due to a germline mutation in about 40% of patients (30% de novo mutation and 10% transmission from an affected parent) and in a non-hereditary form due to a somatic mutation. The retinoblastoma gene is located on chromosome 13q14. This large gene of about 180 kb, consists of 27 exons of rather different sizes and encodes a 4.7 kb transcript with important function in cell cycle regulation. Individuals with bilateral, multifocal tumors are assumed to carry a germline mutation, whereas unilateral and unifocal tumors are generally due to the somatic form. Both copies of the *RB1* gene must be in inactivated before a tumor develops. In about half of patients with the germline mutation the second event inactivating the second allele can be shown by loss of heterozygosity in tumor tissues compared to surrounding somatic tissues.

Knowledge of the *RB1* gene locus affords an opportunity to specify the type of mutation in many patients and arrive at a definitive molecular diagnosis. This is the basis for clinical evaluation and genetic counseling. The types of mutation are large scale deletions, small deletions and insertions, and base substitutions. There is no hot-spot for mutations.

During the last several years we have studied more than 200 patients in search for large scale and small deletions and insertions, and missense mutations. Using intragenic polymorphic DNA markers we were able to identify the mutant haplotype in all familial cases. Direct DNA analysis identified a mutation in about 25% of patients. The distribution of lesions will be described in relation to the clinical situation.

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