

Cancer Prone Disease Section

Mini Review

Retinoblastoma

Dietmar R Lohmann

Institut fuer Humangenetik, Hufelandstr. 55, D-45122 Essen, Germany (DRL)

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Identity

Inheritance

Predisposition to retinoblastoma is transmitted as an autosomal dominant trait; it is caused by mutations in the RB1 gene; penetrance and expressivity depend on the nature of the predisposing mutational change; there is also a non-hereditary form of retinoblastoma (mostly in children with isolated unilateral retinoblastoma) that is caused by RB1-mutations confined to somatic cells.

Clinics

Phenotype and clinics

Retinoblastoma in early childhood: white reflexes in one or both eyes or strabismus usually are the first signs indicating this malignant eye tumour; in most children with the hereditary retinoblastoma, both eyes are affected by multiple tumour foci (bilateral multifocal retinoblastoma).

Adults (most often relatives of patients with retinoblastoma) may show retinal scars indicating regressed retinoblastomas or retinomas (non-progressive tumours).

In addition to retinoblastoma, children with cytogenetic deletions involving 13q14 may show developmental delay and dysmorphic signs.

Neoplastic risk

Early childhood: formation of retinoblastomas (see genotype-phenotype correlation).

Adolescence and adulthood: tumours outside the eye (second primary neoplasms):

- osteosarcoma,
- melanoma,

- brain tumours (pinealoma in particular some patients also show multiple benign tumours of adipose tissue (lipoma).

Treatment

Retinoblastomas can be cured by (depending on size and location): local therapy (photocoagulation, cryotherapy, radiation), combined systemic and local therapy, or enucleation of the eye; surveillance: following the diagnosis of retinoblastoma, repeated examinations under general anesthesia are required for early diagnosis of new tumour foci; up to now, no screening for second primary neoplasms.

Prognosis

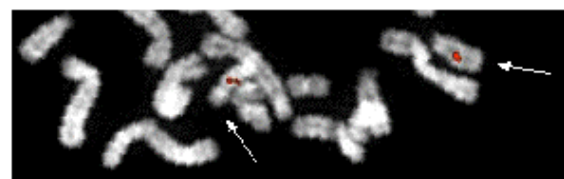
Most often, treatment of retinoblastoma is very effective and, therefore, death from retinoblastoma is rare; however, life span in patients that develop second primary neoplasms is reduced (cumulative mortality at age 40: 6.4% in bilateral patients without radiotherapy, 1.5% in patients with unilateral retinoblastoma).

Genes involved and proteins

RB1 (retinoblastoma susceptibility gene)

Location: 13q14

DNA/RNA



c-RB1 at 13q14 in normal cells: PAC 825K21 - Courtesy Mariano Rocchi.

Description: 180 kb genomic DNA containing 27 exons.

Transcription: 4.7 kb mRNA with 2.7 kb open reading frame.

Protein

Description: 928 aa nuclear phosphoprotein.

Localisation: Nucleus.

Function: Involved in cell cycle regulation.

Mutations

Note: Mutations predisposing to retinoblastoma are one allele mutations; in retinoblastoma, both copies of the RB1 gene are mutated (two-step inactivation mechanism typical of tumor suppressor genes).

Nature and localization of individual mutations are heterogeneous regarding their nature: 20% deletions larger 1kb; 30% small deletions or insertions; 45% point mutations.

And location: mutations have been found in 25 of the 27 coding exons and in promoter elements.

Genotype-phenotype correlation: most mutant RB1-alleles show premature termination codons; typically, these mutant alleles are associated with almost complete penetrance (>95%) and high expressivity (more than 6 individual retinoblastoma foci per individual and, therefore, most often involvement of both eyes); some rare mutant alleles that code for proteins with retention of parts of the functions of the wild-type protein or that result in diminished amounts of wild-type transcript are associated with incomplete penetrance (<75%) and low expressivity (mean of less than 2 tumor foci).

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