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Review

Retinoblastoma (hereditary predisposition)

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Abstract

Review on Retinoblastoma, with data on clinics, and the gene involved.

Keywords
Retinoblastoma, RB1, pRB, tumor suppressor, cell cycle regulation, leukokoria, retinoma, sarcoma, melanoma, brain tumors, reduced penetrance.

Identity

Inheritance
Predisposition to retinoblastoma is transmitted as an autosomal dominant trait trait with incomplete penetrance (Vogel F, 1979; Eloy P et al., 2016; Imperatore V et al., 2018);; it is caused by mutations in the RB1 gene; 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

Retinoblastoma (RB) is the most common intraocular tumor in children, affecting about 1 in 15,000 to 20,000 live births (Broaddus E et al., 2009). It is caused by biallelic inactivation of RB1 gene located at 13q14.2 (Knudson AG Jr, 1971; Friend SH et al., 1986).

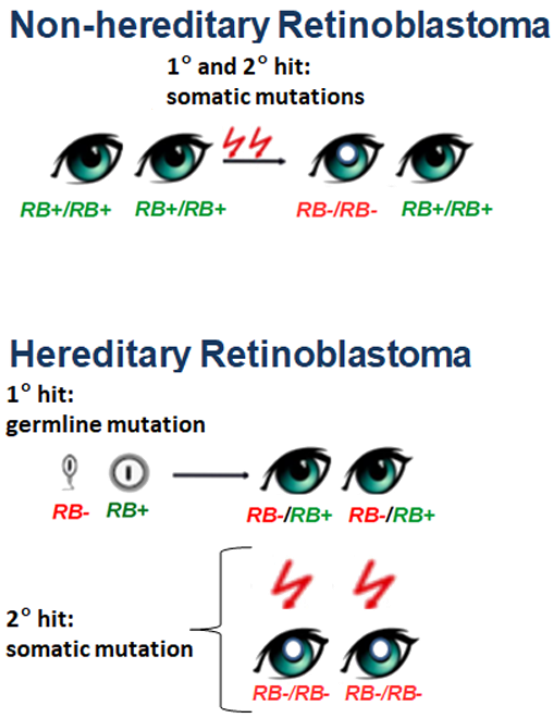


Figure 1. In the non-hereditary form of retinoblastoma, the two RB1 mutations occur in somatic retinal cells. Only one eye is affected. Hereditary retinoblastoma arises when the first mutation is inherited via germinal cells. Tumor foci are initiated by the second mutation in somatic retinal cells. Many children with hereditable RB have new germinal mutations, and both parents are normal. Tumors may be unilateral or bilateral.

The most frequent form is the non hereditary one (60%), with both inactivating events occurring in retinal cells. In this form, the tumor is unilateral with onset after the first year of life in the majority of cases.
The hereditary form (40%) is due to a RB1 germline predisposing mutation and subsequent somatic inactivation of the other allele. This form is generally multifocal and/or bilateral with an anticipation of the mean age of diagnosis (within the first year of life). Hereditary RB is transmitted according to an autosomal dominant pattern with incomplete penetrance, generally reported as equal to 90%. A significant fraction of mutation carriers remain unaffected or develop only benign lesions called retinomas (Harbour JW, 2001).

Phenotype and clinics

Retinoblastoma in early childhood: white pupillary reflexes (leukocoria) in one or both eyes or strabismus usually are the first signs indicating this malignant eye tumour; other signs include glaucoma, inflammation and poor visual tracking (Abramson DH et al., 1998); 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 indicative of a benign lesion called (non-progressive tumours).
In addition to retinoblastoma, children with cytogenetic deletions involving 13q14 may show developmental delay and dysmorphic signs.

Differential_diagnosis

Coats' disease
Persistent hyperplastic primary vitreous (PHPV)
Ocular toxocariasis
Other retinal tumors such as astrocytic hamartoma or medulloepithelioma
Hereditary disorders including tuberous sclerosis complex, Norrie disease, incontinentia pigmenti, familial exudative vitreoretinopathy, and von Hippel-Lindau syndrome

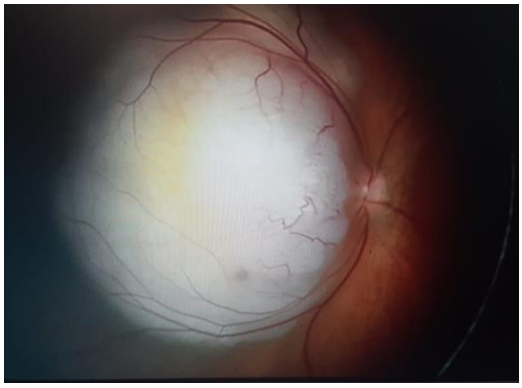


Figure 2. Ophtalmoscopic evaluation of 15X15 mm macular retinoblastoma (stage B).

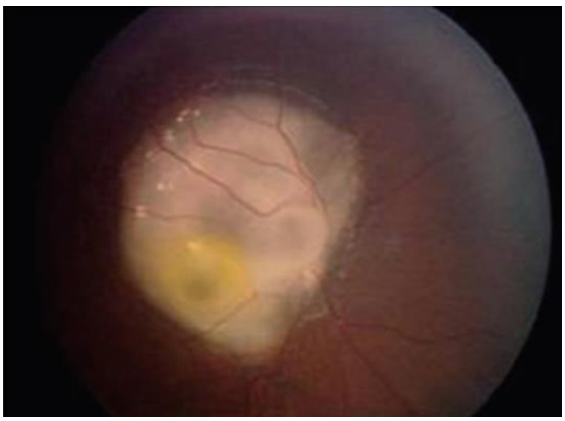


Figure 3. Ophthalmoscopic examination of cystic retinoma on the right fundus oculi overwhelming the optic nerve head.

Neoplastic risk

Early childhood: formation of retinoblastomas Adolescence and adulthood: tumors 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

Tumor stage, localization/size of the tumor, number of foci, presence of vitreous seeding and the age of the child can influence the treatment of RB.
On the basis of these factors, therapeutic approaches can include focal cryotherapy, laser surgery, radiotherapy or chemotherapy.
More recently, intra-arterial selective infusion of chemotherapy in the ophthalmic artery has been introduced (Peterson EC et al., 2011; Venturi C et al., 2013).
However, enucleation (removal of the entire eye) is still the standard treatment for advanced intraocular RB, since it is effective in preventing progression to clinical metastatic disease in 95% of cases (Balmer A et al., 2006).
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).

Cytogenetics

Inborn conditions

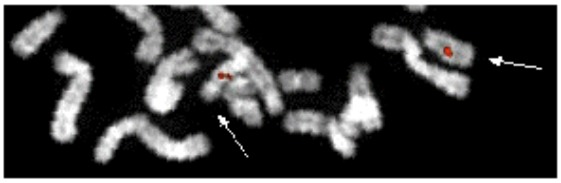
Large-sized molecular deletions including RB1 have been found in 10% of cases causing a contiguous gene deletion syndrome characterized by retinoblastoma, developmental abnormalities and peculiar facial dysmorphisms such as cranial anomalies, frontal bossing, deeply grooved and long philtrum, depressed and broad nasal bridge, bulbous tip of the nose, thin upper lip, broad cheeks, and large ears and lobules (Kloss et al., 1991; Bojinova RI et al., 2001; Lohmann and Gallie 2004; Albrecht P et al., 2005; Caselli R et al., 2007). Few cases of complex translocations resulting in retinoblastoma are reported, and chromosomes involved of balanced reciprocal translocations with 13q14 include 1, 2, 18, 20, and X (Cross HE et al., 1977; Kajii T et al., 1985; Keith CG et al., 1985; Blanquet V et al., 1987; Trivino E et al., 1997; Laquis SJ et al., 2002; Dries D et al., 2003; Huddleston S et al., 2013).

Genes involved and proteins

RB1 (retinoblastoma)

Location

13q14.2



Alias

p105-Rb

DNA/RNA

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 amino acids nuclear phosphoprotein.

Expression

In most tissues.

Localisation

nucleus

Function

Involved in cell cycle regulation, heterochromatin formation, maintenance of genome stability, regulation of cell differentiation and apoptosis (Dimaras H et al., 2015; Dyson NJ et al., 2016).

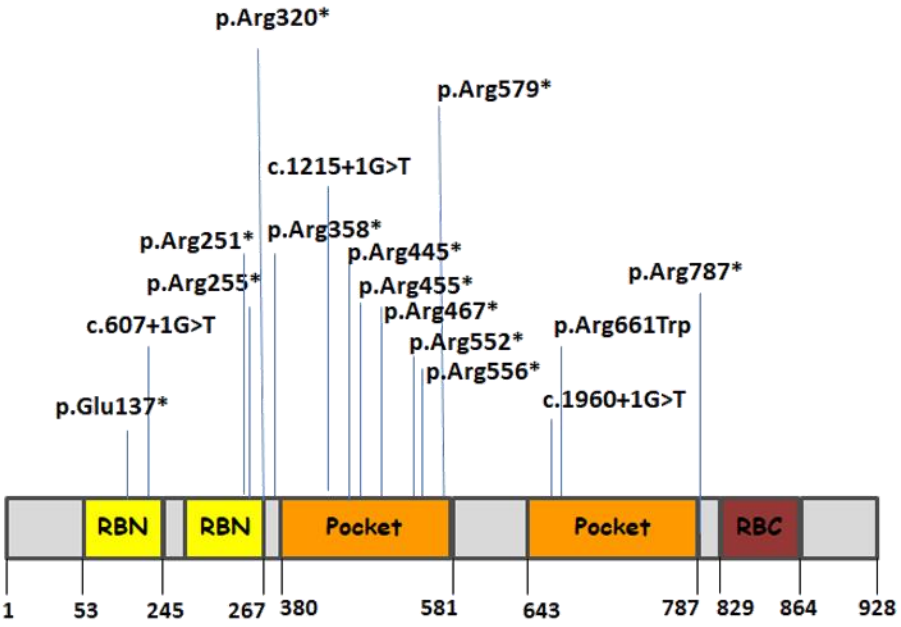


Figure 4. Schematic representation of the pRB protein with the sixteen recurrent mutations. RBN, amino-terminal domain; pocket domains (A and B); RBC, RB carboxy-terminal domain.

Mutations

Germinal

More than 1,700 different mutations, ranging from single nucleotide changes to large deletions, have been listed in the RB1 Gene Mutation Database (http://rb1-lovd.d-lohmann.de). A large fraction (~40%) of mutations are recurrent and consist in sixteen hot spots, including twelve nonsense, one missense and three splicing mutations (Valverde JR et al., 2005). Remaining mutations are scattered along the 27 exons, the promoter and intronic regions (splice site and deep intronic mutations). Complete inactivation of the protein is the result of the majority of RB1 mutations (complete loss of function, amorphic mutations). These mutations, mostly represented by nonsense and frameshift changes resulting in premature termination codons (PTC), are generally associated with full penetrance (Valverde JR et al., 2005). RB1 amorphic mutations can be associated to reduced penetrance in association with somatic mosaicism (Imperatore V et al., 2018). Hypomorphic mutations partially inactivating protein function or reducing gene expression combined with a parent-of-origin effect can also be associated to incomplete penetrance or variable expressivity (Kanber D et al., 2009; Eloy P et al., 2016; Imperatore V et al., 2018). Another important class of RB1 oncogenic events is represented by large rearrangements (~15%; Taylor M et al., 2007). They can include only the RB1 gene (entire or a portion) or be a part of a larger contiguous deletion involving other genes. Whole gene deletions are associated to the development of fewer tumors (Albrecht P, et al. 2005; Taylor M et al., 2007). A minimal genomic region associated with low penetrance has been defined and MED4 has been identified as a gene fundamental for the survival of RB1-/- tumor cells (Dehainault C et al., 2014).

Somatic

In the majority of retinoblastoma tissues, the mutations that result in biallelic inactivation of the RB1 gene are accompanied by loss of constitutional heterozygosity (LOH), originating from deletions and several chromosomal mechanisms such as mitotic recombination and nondisjunction (Cavenee WK et al., 1983; Zhu X et al., 1992; Hagstrom SA and Dryja TP, 1999; Lohmann DR et al., 1997). RB1 promoter hypermethylation is observed in about 13% of retinoblastomas (Greger V et al., 1994; Ohtani-Fujita N et al., 1997; Klutz M et al., 1999).

Epigenetics

In 2009 a 1.2 kb CpG island inside intron 2 (CpG 85) of RB1 was found to show parent-of-origin specific methylation (Kanber D et al., 2009). It is methylated on the maternal chromosome 13 and acts as a weak promoter for an alternative RB1 transcript on the paternal chromosome 13. Paternal mRNA levels are reduced as the result of transcriptional interference of the regular promoter resulting in a ~3 fold excess of the RB1 maternal canonical transcript. As a consequence, RB1 maternally inherited pathogenic variants with hypomorphic effect can retain sufficient suppressor activity to prevent tumor development.

In retinoblastoma tissues methylation of a CpG island (CpG106) encompassing the promoter region of RB1 is a quite frequent mechanism inactivating one copy of the gene (Greger et al., 1994). The same predisposing event in patients' non tumor cells has been rarely described (Jones et al., 1997; Gelli E et al. 2019).

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