

Retinoblastoma

Authors: Dietmar R Lohmann, MD; N Bornfeld, MD; B Horsthemke, PhD; E Passarge, MD
Universitätsklinikum Essen

Posted: 17 July 2000

Summary

Disease characteristics. Retinoblastoma (RB) is a malignant tumor of the developing retina that occurs in children, usually before the age of five years. RB occurs in cells that have cancer-predisposing mutations in both copies of the gene *RB1*. Retinoblastoma may be unifocal or multifocal. About 60% of patients have unilateral RB with a mean age of diagnosis of 24 months; about 40% have bilateral RB with a mean age of diagnosis of 15 months. Patients heterozygous for a cancer-predisposing mutation in one *RB1* allele are said to have a germline mutation and thus have a hereditary predisposition to RB; they are at increased risk of developing other RB-related (non-ocular) tumors. Early diagnosis and treatment of RB and RB-related tumors can reduce morbidity and increase longevity.

Diagnosis/testing. The clinical diagnosis of retinoblastoma is usually established by examination of the fundus of the eye using indirect ophthalmoscopy. Imaging studies can be used to support the diagnosis and stage the tumor. Mutation analysis of the *RB1* gene (chromosomal locus 13q14) in white blood cell DNA is available in clinical laboratories and can identify a germline mutation in about 80% of individuals with a hereditary predisposition to RB. The probability that an *RB1* gene mutation will be detected in an index case depends upon whether the tumor is unifocal or multifocal, whether the family history is positive or negative, and the sensitivity of the testing methodology.

Genetic counseling. Predisposition to retinoblastoma is caused by germline mutations in the *RB1* gene and is transmitted in an autosomal dominant manner. The risks to family members of an index case with RB depend upon whether or not the proband has a germline *RB1* mutation. Molecular genetic testing of DNA from the proband's white blood cells (or other non-tumorous cells) and retinoblastoma tumor may detect the cancer-predisposing *RB1* mutation; if a germline cancer-predisposing mutation is identified in the proband, *RB1* mutation analysis can be used to clarify the genetic status of at-risk sibs and offspring. If *RB1* mutation analysis is not available or is uninformative, indirect testing using polymorphic loci linked to the *RB1* gene can be used in some families to clarify genetic status of at-risk family members. Empiric recurrence risk estimates can be used in all families in which mutation analysis of *RB1* and linkage analysis are unavailable or uninformative. Prenatal testing is possible if the germline *RB1* mutation in the parent is known or if *RB1* linkage analysis is informative in the family.

Diagnosis

The diagnosis of retinoblastoma (RB) is based on clinical findings. Molecular genetic testing of the *RB1* gene (chromosomal locus 13q14) is used for risk prediction in relatives.

Clinical Diagnosis

The diagnosis of retinoblastoma is usually established by examination of the fundus of the eye using indirect ophthalmoscopy. CT, MRI, and ultrasonography are used to support the diagnosis and stage of the tumor. Retinoblastoma is considered "unifocal" when a single RB tumor is present; it is considered "multifocal" if more than one tumor is present. Multifocal tumors include the occurrence of multiple RB tumors in one eye (unilateral) or the occurrence of RB tumors in both eyes (bilateral). The occurrence of bilateral RB plus a pinealoma is referred to as "trilateral" RB [Shields et al 1991].

Testing

Histopathology. Histopathology is performed on surgically removed eyes.

Chromosome analysis. Cytogenetic analysis of peripheral blood lymphocytes detects deletions or rearrangements involving 13q14 in approximately 5% of patients with unilateral RB and approximately 7.5% of patients with bilateral RB. Cytogenetic resolution at the 600-650 band level is recommended and at least 30 metaphases should be analyzed in order

to detect mosaic aberrations that are present in about 1% of patients [Bunin et al 1989].

Molecular Genetic Testing

Molecular genetic testing is used in individuals with RB with normal cytogenetic studies for risk prediction in relatives. Molecular genetic testing includes mutation analysis of the *RB1* gene (chromosomal locus 13q14) or linkage analysis. Molecular genetic testing is available in only a few clinical laboratories.

Linkage analysis using highly informative microsatellite markers tightly linked with the *RB1* gene can be used in two settings:

- To track the mutant allele in families with more than two affected individuals
- To determine if an individual at risk in a family with only one affected individual has inherited either chromosome 13 present in the affected individual

If the individual at risk does not have either chromosome 13 in common with the affected relative, the individual's risk of developing retinoblastoma decreases to the population risk [Greger et al 1988, Wiggs et al 1988].

Linkage analysis is based upon an accurate clinical diagnosis of RB in the affected family members and understanding of genetic relationships in the family. It is dependent on the availability and willingness of family members to be tested.

About 80% of mutations in the *RB1* gene can be detected using current mutation screening techniques [Lohmann et al 1996] (Table 1).

Table 1. Molecular Genetic Testing Used in Patients with Retinoblastoma

% of Patients	Genetic Mechanism	Test Type	Test Availability
70%	Point mutation in the coding regions of <i>RB1</i> gene	Mutation screening followed by DNA sequencing	Clinical GENETests
~10%	Partial deletion in <i>RB1</i> gene	Microsatellite or Southern blot analysis	
~20%	Unknown - <i>RB1</i> mutation cannot be found by all methods		Research

Testing strategy in a proband. A combination of clinical presentation, family history and mutation analysis is used to determine if a proband has a germline (heritable) mutation or two somatic (non-heritable) mutations (Table 2).

Table 2. Probability of Germline Mutation in a Proband with RB

Family History	Unilateral Retinoblastoma		Bilateral Retinoblastoma	Probability that Two <i>RB1</i> Somatic Mutations are Present in the Tumor	Probability that an <i>RB1</i> Germline Mutation is Present	Probability that an <i>RB1</i> Germline Mutation is Detected in WBC
	Multifocal ¹	Unifocal				
Positive		+		0%	100%	~80%
	+ ²			0%	100%	~80%
			+	0%	100%	~80%
Negative			+	~10%	~90%	~72%
	+			10 to 85%	15 to 90%	8 to 72%
		+		~85%	~15%	~8%

1. Includes unilateral retinoblastoma and related second tumors, such as sarcoma, pinealoma

2. One must distinguish between multiple primary tumors and retinal seeding from a single primary tumor.

For a proband, it is always preferable for molecular genetic testing to be performed on the tumor because the identification of one or both mutant alleles in tumor DNA facilitates the search for a germline *RB1* disease-causing mutation in that individual. When the patient has a single, unilateral (unifocal) tumor and a negative family history, the probability of detecting a germline mutation is so low that laboratories often will not offer germline mutation analysis without analysis of the tumor first. If both disease-causing mutations are identified in the tumor, white blood cells from the patient can be screened.

Note: If a disease-causing *RB1* mutation is found in the white blood cells of the patient, the patient has a high probability of a germline mutation. If neither disease-causing mutation is found in white blood cells, the patient has a low probability of a germline mutation; however, the possibility for the patient to have mosaicism for the disease-causing mutation still exists. Thus, absence of an *RB1* disease-causing mutation in white blood cells reduces the probability that the patient has a

mutation in his/her germline, but can not eliminate it.

Clinical Description

Probands with retinoblastoma usually present in one of the following clinical settings:

- Chromosome deletion involving band of 13q14 : Up to 5% of all index cases with unifocal RB and 7.5% of all index cases with multifocal RB have a chromosomal deletion of 13q14. Such chromosomal abnormalities are often associated with developmental delay and birth defects [[Baud et al 1999](#)].
- Normal cytogenetic study and one of the following:
 - Positive family history and unilateral or bilateral RB: ~10% of index cases
 - Negative family history and multifocal RB: 30% of such index cases
 - Negative family history and unifocal RB: 60% of index cases

About 60% of patients have unilateral retinoblastoma with a mean age at diagnosis of 24 months. About 30% have bilateral retinoblastoma, with a mean age of diagnosis of 15 months.

The most common presenting sign of RB is a white pupillary reflex (leukocoria). Strabismus is the second most common presenting sign and may accompany or precede leukocoria. Unusual presenting symptoms include glaucoma, orbital cellulitis, uveitis, hyphema or vitreous hemorrhage [[Balmer et al 1993](#)]. Most affected children are diagnosed under the age of five years. Atypical manifestations are more frequent in older children. Some individuals predisposed to retinoblastoma develop retinal tumors (retinocytoma, retinoma) that undergo spontaneous growth arrest [[Gallie et al 1982](#)].

In most children with bilateral tumors, both eyes are affected at the time of initial diagnosis [[Abramson et al 1992](#)]. Some children who are initially diagnosed with unilateral retinoblastoma later develop a tumor in the contralateral unaffected eye [[Abramson et al 1994](#)].

Retinoma-associated eye lesions. These lesions range from retinal scars to calcified phthisical eyes resulting from spontaneous regression of retinoblastoma [[Balmer et al 1991](#)], and include benign retinal tumors called retinocytoma or retinoma that have undergone spontaneous growth arrest [[Gallie et al 1982](#)].

Related tumors. Patients with germline *RB1* mutations are at an increased risk of developing tumors outside the eye. Pinealomas occur in "retinal-like" tissue in the pineal gland of the brain. Co-occurrence of pinealomas together with retinoblastoma is referred to as trilateral retinoblastoma. Pinealoma is rare; however, unlike retinoblastoma of the eye, which is generally curable, it is usually fatal [[Kivela 1999](#)].

There is also an increased risk of specific other extraocular primary neoplasms (collectively called second primary tumors). Most of the second primary cancers are osteosarcomas, soft tissue sarcomas, or melanomas [[Eng et al 1993](#)]. These tumors usually become manifest in adolescence or adulthood. The incidence of second primary tumors is increased to more than 50% in patients who have received external-beam radiation [[Wong et al 1997](#)].

Genotype-Phenotype Correlations

In the majority of families with retinoblastoma, all members who have inherited a germline mutation develop multiple tumors in both eyes. It is not unusual to find, however, that the first affected member has only unilateral retinoblastoma. Most of these families segregate *RB1* null alleles that are altered by frameshift or nonsense mutations. With few specific exceptions, *RB1* null alleles show nearly complete penetrance (greater than 99%) [[Lohmann et al 1996](#), [Sippel et al 1998](#), and unpublished data].

Rarely, some families have a "low penetrance" phenotype with reduced expressivity (i.e., increased prevalence of unilateral retinoblastoma) and incomplete penetrance (25% and lower) [[Macklin 1960](#)]. This low penetrance phenotype was found to be associated with mutant *RB1* alleles showing distinct in-frame or missense changes or mutations in the promoter region of the *RB1* gene [[Sakai et al 1991](#), [Hogg et al 1992](#), [Dryja et al 1993](#), [Lohmann et al 1994](#)]. A third category of families shows reduced penetrance but no reduced expressivity in family members with retinoblastoma.

Cytogenetically visible deletions involving 13q14 that also result in deletions of other genes in the same chromosomal region in addition to the *RB1* gene may cause developmental delay and mild to moderate facial dysmorphism [[Brown et al 1993](#)]. As sizeable deletions of 13q14 show reduced expressivity, a considerable proportion of patients with such deletions show unilateral retinoblastoma only and some of these children develop no tumor at all [[Matsunaga 1980](#)].

Prevalence

The incidence of retinoblastoma is estimated to be between one in 15,000 and one in 20,000 live births [[Devesa 1975](#), [Suckling et al 1982](#), [Moll et al 1997](#)].

Differential Diagnosis

Several ocular conditions of childhood can clinically simulate retinoblastoma:

- Sporadic congenital disorders such as persistent hyperplastic primary vitreous and Coat's disease
- Hereditary disorders such as [tuberous sclerosis](#), [Norrie disease](#), [incontinentia pigmenti](#), and familial exudative vitreoretinopathy
- Ocular infestation by *Toxocara canis* [[Shields et al 1991](#)]

Management

Management is focused on the following:

- Treatment of retinoblastoma and routine surveillance of affected individuals for early detection of second ocular and non-ocular tumors
- Surveillance of at-risk children for early detection and treatment of retinoblastoma [[Greger et al 1988](#)]

Affected Individuals

Treatment of retinoblastoma. Goals of treatment are preservation of sight and life. Prior to the planning of therapy, the extent of the tumor within and outside the eye should be determined. In addition to tumor stage, choice of treatment depends on several factors including the number of tumor foci (unifocal, unilateral multifocal, or bilateral disease), localization and size of the tumor(s) within the eye, presence of vitreous seeding, and the age of the child.

Treatment options include enucleation, cryotherapy, photocoagulation, photochemistry, external-beam radiation, and radiation therapy using episcleral plaques. Novel treatment options include systemic chemotherapy combined with local therapy [[Gallie et al 1996](#), [Bornfeld et al 1997](#)]. As optimum treatment may be complex, specialists skilled in the treatment of retinoblastoma from various fields including ophthalmology, pediatric ophthalmology, radiation oncology, and oncology often are included.

Detection of second ocular tumors. Following successful treatment, children require frequent follow-up examinations for early detection of new intraocular tumors [[Abramson et al 1992](#), [Abramson et al 1994](#)].

- It is recommended that children have an eye examination every three months until age five years. Young or uncooperative children usually require examination under anesthesia.
- All patients who have unilateral retinoblastoma are at risk. Even patients identified to have *RB1* cancer-predisposing mutations in a tumor and no evidence of a germline *RB1* cancer-predisposing mutation remain at risk of developing additional tumors because of possible mosaicism for the *RB1* allele [[Lohmann et al 1997](#), [Sippel et al 1998](#)]. Therefore, absence of an *RB1* mutation in white blood cell DNA of such patients cannot be used to limit the surveillance for second tumors.

Detection of second non-ocular tumors. Because of the high risk of sarcomas, the physician and parents should evaluate complaints of bone pain or lumps promptly. No specific screening protocols exist.

At-Risk Individuals

Early recognition of RB may allow for timely intervention and improved final outcome. Individuals who warrant surveillance for early manifestations of RB include the following:

- Individuals with retinomas [[Eagle et al 1989](#)]
- Asymptomatic at-risk children. Use of DNA-based testing for early identification of at-risk family members (see [Genetic Counseling](#)) improves diagnostic certainty and reduces the need for costly screening procedures in those at-risk family members who have not inherited the disease-causing mutation [[Noorani et al 1996](#)]. ASCO, the American Society of Clinical Oncologists, identifies RB as a Group 1 disorder, i.e., a hereditary syndrome for which genetic testing is considered part of the standard management for at-risk family members [[ASCO policy statement](#)].

Recommendations for surveillance of children who have inherited an *RB1* disease-causing mutation OR children at risk for RB who have not undergone molecular genetic testing:

- Eye examinations by an ophthalmologist experienced in the treatment of retinoblastoma starting directly after birth and occurring every three months until age five years. Young or uncooperative children may require examination under anesthesia.

Recommendations for surveillance of at-risk children who have not inherited the disease-causing mutation as determined by *RB1* mutation analysis or linkage analysis:

- Examination by an ophthalmologist familiar with retinoblastoma shortly after birth. Subsequent eye examinations should be performed as needed for routine pediatric care.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal or cultural issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see [GENETests](#). -ED.

Mode of Inheritance

Germline *RB1* mutations are transmitted in an autosomal dominant manner. Tumor development starts from cells that do not have a normal *RB1* allele.

Risk To Family Members

Parents of a proband. The recommendations for determining the genetic status of the parent of an index case with retinoblastoma or the conclusions about the genetic status of the parent depend upon the following in the index case:

- **Cytogenetically detectable chromosome 13 deletion or rearrangement. Recommendation:** Parental cytogenetic studies to determine if either parent carries a balanced chromosome translocation or rearrangement
- **Positive family history** (i.e., the parent had retinoblastoma or a close relative of one parent had retinoblastoma). **Conclusion:** The parent has an *RB1* cancer-predisposing germline mutation
- **Negative family history. Recommendation:** Examination of apparently unaffected parents by an ophthalmologist knowledgeable about retinoblastoma, retinoma, and retinoblastoma-associated eye lesions. If such a lesion is detected, the parent has an *RB1* cancer-predisposing germline mutation
- **Presence of a germline *RB1* cancer-predisposing mutation. Recommendation:** Molecular genetic testing of a blood sample of both parents. **Conclusion:**
 - If a germline mutation is identified in either parent, the parent is at risk of developing non-ocular second primary tumors and is at-risk to transmit the mutation to other offspring.
 - If a germline *RB1* mutation is not identified in either parent, two possibilities exist: 1) the index case has a *de novo* *RB1* germline mutation (90-94% chance); or 2) one parent has mosaicism (which includes the germline) for the *RB1* cancer-predisposing mutation (6-10% chance).
- **Mosaicism for an *RB1* cancer-predisposing mutation. Recommendation:** Molecular genetic testing of the parents is not necessary.

Sibs of a proband. The risk to sibs of an index case depends on the genetic status of the parents of the index case.

- If a parent is determined to have a germline *RB1* cancer-predisposing mutation either by positive family history, by an eye examination that reveals a retinoblastoma-associated eye lesion, or by molecular genetic testing that reveals the presence of a cancer-predisposing *RB1* mutation, the risk to each sib of the index case is 50% (or lower if the carrier parent is a mutational mosaic) of inheriting the cancer-predisposing *RB1* mutation. Given the approximately 99% penetrance of most *RB1* cancer-predisposing mutations, the actual risk for retinoblastoma in these individuals is about 50% (or lower if the carrier parent is a mutational mosaic). (Note: In rare families with "familial-low penetrance retinoblastoma," the risk of tumor development is less than 40%) [[Sakai et al 1991](#), [Lohmann et al 1994](#)].
- If neither parent has the cancer-predisposing *RB1* mutation that was identified in the index case, germline mosaicism in one parent is possible and the risk to each sib of having retinoblastoma is 3-5% [[Sippel et al 1998](#)].
- If the index case has mosaicism for an *RB1* cancer-predisposing mutation, it is assumed that the mutation arose as a post-zygotic event and that neither parent has an *RB1* germline mutation. The risk to the sibs is not increased.
- If molecular genetic testing is not available or is uninformative, empiric risks based on tumor presentation (i.e., unifocal or multifocal) and family history can be used ([Table 3](#)). The low, but not negligible, risk to sibs of an index case with a negative family history presumably reflects the presence of either a germline *RB1* mutation with reduced penetrance in one parent or somatic mosaicism (that includes the germline) for an *RB1* mutation in one parent.

Offspring of a proband. The risk to the offspring of a proband depends upon the following:

- If the index case has sporadic bilateral RB, a germline *RB1* cancer-predisposing mutation has to be assumed and the risk to each offspring is close to 50%.
- If the index case has had sporadic unilateral multifocal RB, recurrence risk for offspring is lower [[Sippel et al 1998](#)]. (Note: In rare families with "familial-low penetrance retinoblastoma," the risk of tumor development is less than 40%).
- The low (~1%), but not negligible, risk to the offspring of index cases with unifocal disease and a negative family

history reflects the possibility of a germline *RB1* mutation with low penetrance or mutational mosaicism.

Table 3. Empiric Risks for Development of Retinoblastoma in Sibs and Offspring of a Proband when an *RB1* Germline Mutation Has Not Been Identified

Clinical Presentation in Index Case			Family History	Risk to Sibs of an Index Case	Risk to Offspring of an Index Case
Tumor		Bilateral			
Unilateral Multifocal	Unilateral Unifocal				
X			Negative	2% ¹	?50%
	X		Negative	1 to 2% ¹	6 to 50%
		X	Negative	~1%	2 to 6%
		X	Positive	?40%	?40%
X			Positive	50%	50%

1. If there is no unaffected sibling [Draper et al 1992].

Prenatal Testing

Prenatal testing is possible for pregnancies at risk if either a disease-causing *RB1* mutation is known in the affected parent or affected sibling or if linkage analysis is informative. DNA can be extracted from cells obtained by amniocentesis at 16-18 weeks' gestation or by chorionic villus sampling (CVS) at about 10-12 weeks' gestation. The amount of time required to obtain test results should be established before amniocentesis or CVS is performed.

If a disease-causing *RB1* mutation is identified in the fetus, ultrasound examination might be used to determine if preterm delivery is required for early treatment [Gallie et al 1999].

Molecular Genetics

Table 4. Molecular Genetics of Retinoblastoma

Disease Name	Gene Symbol	Locus	Normal Gene Product	Genomic Databases
RB1	<i>RB1</i>	13q14	Retinoblastoma-associated protein	OMIM LocusLink RB1

Molecular Genetic Pathogenesis

- **Gene symbol:** *RB1*
- **Chromosomal locus:** 13q14
- **Normal allelic variants:** 27 exons are transcribed and spliced into a 4.7 kb mRNA. There is no indication of alternative splicing. There are no known polymorphic sites within the 2.7 kb open reading frame, but there are intronic variants and two highly polymorphic microsatellites (Rb1.20, Rbi2) and one minisatellite (RBD).
- **Disease-causing allelic variants:** Over 200 distinct mutations have been reported in white blood cell DNA of patients with retinoblastoma or in tumors. About 80-85% of mutations result in a premature termination codon, usually through single base substitutions, frameshift mutations, or splice mutations. Mutations have been found scattered throughout exon 1 to exon 25 of the *RB1* gene and its promoter region. Recurrent mutations are observed at 14 methylated CpG-dinucleotides. About 80% of *de novo* germline mutations are paternal in origin. The reasons for the paternal predominance are unknown.
- **Normal gene product:** The *RB1* gene encodes a ubiquitously expressed nuclear protein that is involved in cell cycle regulation (G1 to S transition). The RB-protein is phosphorylated by members of the cyclin-dependent kinase (cdk) system prior to the entry into S-phase. Upon phosphorylation, the binding activity of the pocket domain is lost, resulting in the release of cellular proteins. (For a review see [Weinberg 1995](#))
- **Abnormal gene product:** The majority of mutant alleles, if expressed at all, code for proteins that have lost cell cycle regulating functions. Retention of partial activities has been observed in proteins resulting from mutant alleles that are associated with low penetrance retinoblastoma [[Kratzke et al 1994](#), [Bremner et al 1997](#), [Otterson et al 1997](#)].

Resources

GeneClinics provides information about selected national organizations and resources for the benefit of the reader. GeneClinics is not responsible for information provided by other organizations. -ED.

- **A Parent's Guide to Understanding Retinoblastoma**

www.retinoblastoma.com/guide/guide.html

- **National Retinoblastoma Parents Group**

PO Box 317

Watertown, MA 02471

Phone: 800-562-6265

Fax: 617-972-7444

Email: napvi@perkins.pvt.k12.ma.us

- **The Retinoblastoma Society**

Saint Bartholomew's Hospital

London, EC1A 7BE, UK

Phone: 020 7600 3309

Fax: 020 7600 8579

ds.dial.pipex.com/rbinfo

- **Candlelighters Childhood Cancer Foundation**

3910 Warner St

Kensington, MD 20895

Phone: 800-366-2223; 301-962-3520

Email: info@candlelighters.org

www.candlelighters.org

- **National Federation of the Blind**

1800 Johnson Street

Baltimore, MD 21230

Phone: 410-659-9314

Fax: 410-685-5653

Email: nfb@iamdigek.net

www.nfb.org

- **NCBI Genes and Disease Webpage**

www.ncbi.nlm.nih.gov/disease/Retinoblast.html

References

Statements and Policies Regarding Genetic Testing

- Statement of the American Society of Clinical Oncology: [Genetic Testing for Cancer Susceptibility](#)

MEDLINE Articles on Retinoblastoma

[About GeneClinics Custom Searches](#)

Literature Cited

- Abramson DH, Gamell LS, Ellsworth RM, Kruger EF, Servodidio CA, Turner L, Sussman D (1994) Unilateral retinoblastoma: new intraocular tumours after treatment. *Br J Ophthalmol* 78:698-701 [[Medline](#)]
- Abramson DH, Greenfield DS, Ellsworth RM (1992) Bilateral retinoblastoma. Correlations between age at diagnosis and time course for new intraocular tumors. *Ophthalmic Paediatr Genet* 13:1-7 [[Medline](#)]
- Balmer A, Gailloud C, Munier F, Uffer S, Guex-Crosier Y (1993) Retinoblastoma. Unusual warning and clinical signs. *Ophthalmic Paediatr Genet* 14:33-8 [[Medline](#)]
- Balmer A, Munier F, Gailloud C (1991) Retinoma. Case studies. *Ophthalmic Paediatr Genet* 12:131-7 [[Medline](#)]
- Baud O, Cormier-Daire V, Lyonnet S, Desjardins L, Turleau C, Doz F (1999) Dysmorphic phenotype and neurological impairment in 22 retinoblastoma patients with constitutional cytogenetic 13q deletion. *Clin Genet* 55:478-82 [[Medline](#)]
- Bornfeld N, Schuler A, Bechrakis N, Henze G, Havers W (1997) Preliminary results of primary chemotherapy in retinoblastoma. *Klin Padiatr* 209:216-21 [[Medline](#)]
- Bremner R, Du DC, Connolly-Wilson MJ, Bridge P, Ahmad KF, Mostachfi H, Rushlow D, Dunn JM, Gallie BL (1997) Deletion of RB exons 24 and 25 causes low-penetrance retinoblastoma. *Am J Hum Genet* 61:556-70 [[Medline](#)]

- Brown S, Gersen S, Anyane-Yeboah K, Warburton D (1993) Preliminary definition of a "critical region" of chromosome 13 in q32: report of 14 cases with 13q deletions and review of the literature. *Am J Med Genet* 45:52-9 [[Medline](#)]
- Bunin GR, Emanuel BS, Meadows AT, Buckley JD, Woods WG, Hammond GD (1989) Frequency of 13q abnormalities among 203 patients with retinoblastoma. *J Natl Cancer Inst* 81:370-4 [[Medline](#)]
- Carlson EA, Desnick RJ (1979) Mutational mosaicism and genetic counseling in retinoblastoma. *Am J Med Genet* 4:365-81 [[Medline](#)]
- Devesa SS (1975) The incidence of retinoblastoma. *Am J Ophthalmol* 80:263-5 [[Medline](#)]
- Draper GJ, Sanders BM, Brownbill PA, Hawkins MM (1992) Patterns of risk of hereditary retinoblastoma and applications to genetic counselling. *Br J Cancer* 66:211-9 [[Medline](#)]
- Dryja TP, Rapaport J, McGee TL, Nork TM, Schwartz TL (1993) Molecular etiology of low-penetrance retinoblastoma in two pedigrees. *Am J Hum Genet* 52:1122-8 [[Medline](#)]
- Eagle RC Jr, Shields JA, Donoso L, Milner RS (1989) Malignant transformation of spontaneously regressed retinoblastoma, retinoma/retinocytoma variant. *Ophthalmology* 96:1389-95 [[Medline](#)]
- Eng C, Li FP, Abramson DH, Ellsworth RM, Wong FL, Goldman MB, Seddon J, Tarbell N, Boice JD Jr (1993) Mortality from second tumors among long-term survivors of retinoblastoma *J Natl Cancer Inst* 85:1121-8 [[Medline](#)]
- Gallie BL, Budning A, DeBoer G, Thiessen JJ, Koren G, Verjee Z, Ling V, Chan HS (1996) Chemotherapy with focal therapy can cure intraocular retinoblastoma without radiotherapy [published erratum appears in *Arch Ophthalmol* 1997 Apr; 115(4):525] *Arch Ophthalmol* 114:1321-8 [[Medline](#)]
- Gallie BL, Ellsworth RM, Abramson DH, Phillips RA (1982) Retinoma: spontaneous regression of retinoblastoma or benign manifestation of the mutation? *Br J Cancer* 45:513-21 [[Medline](#)]
- Gallie BL, Gardiner JA, Toi A, Heon E, Chan H, Sutherland J, MacKeen L, Anderson J, Han L, Budning A, Sermer M (1999) Retinoblastoma treatment in premature infants diagnosed prenatally by ultrasound and molecular analysis. *Am J Hum Genet* 66:A62
- Greger V, Kerst S, Messmer E, Hopping W, Passarge E, Horsthemke B (1988) Application of linkage analysis to genetic counselling in families with hereditary retinoblastoma. *J Med Genet* 25:217-21 [[Medline](#)]
- Hogg A, Onadim Z, Baird PN, Cowell JK (1992) Detection of heterozygous mutations in the RB1 gene in retinoblastoma patients using single-strand conformation polymorphism analysis and polymerase chain reaction sequencing. *Oncogene* 7:1445-51 [[Medline](#)]
- Kivela T (1999) Trilateral retinoblastoma: a meta-analysis of hereditary retinoblastoma associated with primary ectopic intracranial retinoblastoma [see comments] *J Clin Oncol* 17:1829-37 [[Medline](#)]
- Kratzke RA, Otterson GA, Hogg A, Coxon AB, Geradts J, Cowell JK, Kaye FJ (1994) Partial inactivation of the RB product in a family with incomplete penetrance of familial retinoblastoma and benign retinal tumors. *Oncogene* 9:1321-6 [[Medline](#)]
- Lohmann DR, Brandt B, Hopping W, Passarge E, Horsthemke B (1994) Distinct RB1 gene mutations with low penetrance in hereditary retinoblastoma. *Hum Genet* 94:349-54 [[Medline](#)]
- Lohmann DR, Brandt B, Hopping W, Passarge E, Horsthemke B (1996) The spectrum of RB1 germ-line mutations in hereditary retinoblastoma. *Am J Hum Genet* 58:940-9 [[Medline](#)]
- Lohmann DR, Gerick M, Brandt B, Oelschlaeger U, Lorenz B, Passarge E, Horsthemke B (1997) Constitutional RB1-gene mutations in patients with isolated unilateral retinoblastoma *Am J Hum Genet* 61:282-94 [[Medline](#)]
- Macklin MT (1960) A study of retinoblastoma in Ohio. *Am J Hum Genet* 12:1-43
- Matsunaga E (1980) Retinoblastoma: host resistance and 13q- chromosomal deletion. *Hum Genet* 56:53-8 [[Medline](#)]
- Moll AC, Kuik DJ, Bouter LM, Den Otter W, Bezemer PD, Koten JW, Imhof SM, Kuyt BP, Tan KE (1997) Incidence and survival of retinoblastoma in The Netherlands: a register based study 1862-1995. *Br J Ophthalmol* 81:559-62 [[Medline](#)]
- Noorani HZ, Khan HN, Gallie BL, Detsky AS (1996) Cost comparison of molecular versus conventional screening of relatives at risk for retinoblastoma *Am J Hum Genet* 59:301-7 [[Medline](#)]
- Otterson GA, Chen Wd, Coxon AB, Khleif SN, Kaye FJ (1997) Incomplete penetrance of familial retinoblastoma linked to germ-line mutations that result in partial loss of RB function. *Proc Natl Acad Sci U S A* 94:12036-40 [[Medline](#)]
- Sakai T, Ohtani N, McGee TL, Robbins PD, Dryja TP (1991) Oncogenic germ-line mutations in Sp1 and ATF sites in the

human retinoblastoma gene. *Nature* 353:83-6 [[Medline](#)]

- Shields JA, Shields CL, Parsons HM (1991) Differential diagnosis of retinoblastoma. *Retina* 11:232-43 [[Medline](#)]
- Sippel KC, Fraioli RE, Smith GD, Schalkoff ME, Sutherland J, Gallie BL, Dryja TP (1998) Frequency of somatic and germ-line mosaicism in retinoblastoma: implications for genetic counseling. *Am J Hum Genet* 62:610-9 [[Medline](#)]
- Suckling RD, Fitzgerald PH, Stewart J, Wells E (1982) The incidence and epidemiology of retinoblastoma in New Zealand: A 30- year survey. *Br J Cancer* 46:729-36 [[Medline](#)]
- Weinberg RA (1995) The retinoblastoma protein and cell cycle control. *Cell* 81:323-30 [[Medline](#)]
- Wiggs J, Nordenskjold M, Yandell D, Rapaport J, Grondin V, Janson M, Werelius B, Petersen R, Craft A, Riedel K, et al (1988) Prediction of the risk of hereditary retinoblastoma, using DNA polymorphisms within the retinoblastoma gene. *N Engl J Med* 318: 151-7 [[Medline](#)]
- Wong FL, Boice JD Jr, Abramson DH, Tarone RE, Kleinerman RA, Stovall M, Goldman MB, Seddon JM, Tarbell N, Fraumeni JF Jr, Li FP (1997) Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk *JAMA* 278: 1262-7 [[Medline](#)]

Profile History

Authors

Dietmar R Lohmann, MD [[MEDLINE](#)]
Institut für Humangenetik

B Horsthemke, PhD [[MEDLINE](#)]
Institut für Humangenetik

N Bornfeld, MD [[MEDLINE](#)]
Augenklinik

E Passarge, MD [[MEDLINE](#)]
Institut für Humangenetik

Universitätsklinikum Essen

[About GeneClinics Medline Searches](#)

Last Update/Revision

17 July 2000

Revision History

- 13 Jul 2000: Internal edits (me)
- 04 Jul 2000: Author revisions (me)
- 30 Jun 2000: Reviewer changes (tk)
- 15 Mar 2000: Internal edits; reviewer changes (tk)
- 15 Oct 1999: Internal edits; summary added (pb)
- 06 Oct 1999: Peer review (pb)
- 01 Oct 1999: Peer review (pb)
- 27 Sep 1999: Reviewed (pb)
- 10 Aug 1999: Internal edits (pb)
- 11 Jul 1999: Author revisions (pb)
- 19 Apr 1999: Internal edits (pb)
- 21 Jan 1999: Original submission (pb)

Copyright© 2001, University of Washington, Seattle
All Rights Reserved

Funded by [National Library of Medicine](#), [National Human Genome Research Institute](#), [National Cancer Institute](#), and [Office of Rare Diseases](#) of the NIH

Administrative support from [University of Washington](#), Seattle