GENEReviews

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Retinitis Pigmentosa Overview

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Summary

Disease characteristics. Retinitis pigmentosa (RP) is a group of inherited disorders in which abnormalities of the photoreceptors (rods and cones) or the retinal pigment epithelium (RPE) of the retina lead to progressive visual loss. Affected individuals first experience defective dark adaptation or "night blindness," followed by constriction of the peripheral visual field and, eventually, loss of central vision late in the course of the disease.

Diagnosis/testing. The diagnosis of RP relies upon documentation of progressive loss in photoreceptor function by electroretinography (ERG) and visual field testing. The mode of inheritance of RP is determined by family history. At least 35 different genes or loci are known to cause nonsyndromic RP. DNA testing is available on a clinical basis for *RLBP1* (autosomal recessive, Bothnia type RP), *RP1* (autosomal dominant, RP1), *RHO* (autosomal dominant, RP4), *RDS* (autosomal dominant, RP7), *PRPF8* (autosomal dominant, RP13), *PRPF3* (autosomal dominant, RP18), *CRB1* (autosomal recessive, RP12), *ABCA4* (autosomal recessive, RP19), and *RPE65* (autosomal recessive, RP20). For all other genes, molecular genetic testing is available on a research basis only.

Management. Therapy with vitamin A palmitate may slow retinal degeneration but is not recommended for those under age 18 years and should be routinely monitored in women of childbearing age because of potential teratogenic effects. Use of UV-A and UV-B blocking sunglasses is recommended. Diamox therapy may reduce cystoid macular edema. CPF 550 lenses may increase eye comfort by reducing glare and adaptation time from light to dark. Various other optical aids include magnifiers, closed-circuit television, and high-intensity, wide-beam flashlights.

Genetic counseling. RP can be inherited in an autosomal dominant, autosomal recessive, or X-linked manner. X-linked RP can be either recessive, affecting males only, or dominant, affecting both males and females; females are always more mildly affected. Some digenic and mitochondrial forms have also been described. Genetic counseling depends on an accurate diagnosis, determination of the mode of inheritance in each family, and results of molecular genetic testing.

Definition

Clinical Manifestations

RP refers to a group of inherited disorders in which abnormalities of the photoreceptors (rods and cones) of the retina lead to progressive visual loss.

In RP, loss of rod function predominates early in the clinical course. The initial symptom of RP is usually defective dark adaptation or "night blindness." If individuals with RP do not volunteer a history of faulty dark adaptation, detailed questioning about activities at dusk or with minimal lighting often elicits such a history starting in childhood or adolescence. In general, the earlier the age of onset of defective dark adaptation, the more severe the course of RP. Although mid-peripheral vision loss occurs early in the disease, it is rarely recognized by the affected individual and is usually not a presenting symptom. Affected individuals may be considered "clumsy" before constriction of visual fields (i.e., "tunnel vision") is detected.

Despite the fact that sensitive tests of cone function can document early cone involvement, central **visual acuity** is usually preserved until the end stages of RP. Loss of central visual acuity over time correlates with the presence of macular lesions early in the course [Flynn et al 2001]. Most commonly, central acuity loss is caused by macular atrophy in advanced RP or less commonly from cystoid macular edema, which occurs in some individuals in the early stages of RP. Some investigators have found a general correlation between age-related visual acuity and genetic subtype. Fishman (1978b) found that individuals with autosomal dominant RP had the best prognosis, with the majority of those younger than age 30 years having a visual acuity of 20/30 or better. Males with X-linked RP had the worst prognosis, with all individuals older than age 50 years having a visual acuity lower than 20/200. Individuals with autosomal recessive and simplex RP (i.e., single occurrence in the family) were intermediate in severity. Others have found no correlation between central visual impairment and genetic subtype.

The **fundus appearance** in RP usually depends on the stage of the retinal degeneration. In the earliest stages when electroretinography reveals defective rod responses in individuals who may not yet have appreciated symptoms, the fundus usually appears normal. The term retinitis pigmentosa *sine pigmento* has been used to refer to a normal appearance of the retina despite documented abnormalities of photoreceptor function. The earliest observed changes in the fundus are arteriolar narrowing, fine dust-like intraretinal pigmentation, and loss of pigment from the pigment epithelium. As photoreceptor deterioration progresses, there is increasing loss of pigment from the pigment epithelium with intraretinal clumping of melanin, appearing most often as coarse clumps in a "bone spicule" configuration. Retinal vessel attenuation and waxy pallor of the optic nerve become apparent in individuals with advanced RP. The cause of the retinal vessel attenuation is unknown, but it appears to be a secondary change and not the primary disease process.

Posterior subcapsular cataracts characterized by yellowish crystalline changes in the visual axis of the peripheral lens cortex are common in all forms of RP. Severity of the cataract correlates with the age of the affected individual. The cause of cataract formation in RP is unknown.

Dust-like particles in the vitreous are present in the great majority of individuals with RP. These are fine, colorless particles comprising free melanin pigment granules, pigment epithelium, uveal melanocytes, and macrophage-like cells, which are evenly distributed throughout the vitreous. Observation of these particles can be helpful in the diagnosis of early RP before fundus changes are apparent.

White dots deep in the retina at the level of the pigment epithelium are believed to be a nonspecific manifestation of pigment epithelial degeneration and may account for the retinal appearance termed "retinitis punctata albescens," which is considered a manifestation of RP.

Hyaline bodies (drusen) of the optic nerve head are common and are of no clinical or diagnostic significance.

A rare occurrence in individuals with advanced RP is **exudative vasculopathy** associated with telangiectatic vessels, serous retinal detachment, and lipid deposition in the retina. The cause of exudative vasculopathy in RP is unknown.

Sector RP is a term used to describe changes in one quadrant or one half of each fundus. Most commonly, the inferonasal quadrants are symmetrically involved. The visual field defects are less severe than those of typical RP and correspond to the ophthalmoscopically abnormal retina. Individuals with sector RP usually lack symptoms of defective dark adaptation, although widespread abnormalities of rod and cone function are usually detected by ERG. Information about the natural history of sector RP is conflicting. Sectoral changes have been observed in autosomal dominant RP and in females heterozygous for X-linked RP. The incidence of sector RP is low, either because it is uncommon or because mild symptoms result in infrequent diagnosis.

Establishing the Diagnosis

A consensus conference [Marmor et al 1983] suggested that the diagnosis of RP is established when the following are present:

- Rod dysfunction as measured by
  - Dark adaptation (elevated rod final threshold)

    OR
  - Electroretinogram (ERG) (nondetectable rod responses, or rod responses with reduced amplitude and prolonged implicit time or nondetectable)
- Progressive loss in photoreceptor function
- Loss of peripheral vision
- Bilateral involvement

The retina is assessed through 1) ophthalmoscopy including, when warranted, fluorescein angiography; 2) functional assessment of vision (e.g., visual fields, visual acuity, and color vision); and 3) electrophysiologic testing (electroretinography).

Ophthalmoscopy of the retina in individuals with advanced RP is characterized by the presence of intraretinal clumps of black pigment, markedly attenuated retinal vessels, loss of retinal pigment epithelium (RPE), and pallor of the optic nerve. These changes reflect longstanding retinal degeneration and need not be present to make the diagnosis of RP. The fundus findings are, however, instrumental in distinguishing RP from other retinal dystrophies that have similar clinical findings but distinctive retinal changes.

Functional assessment of vision:

- **Visual field testing,** the mapping of subjectively perceived test objects, which are ellipses of light varying in size from 1/16 mm to 64 mm, projected upon a uniformly illuminated background. Symptomatic defective dark adaptation in individuals with

RP is accompanied by peripheral visual field restriction. In early RP, a ring scotoma (blind spot) is present in the mid-periphery of the visual field ~20-25° from fixation. As the RP progresses, the outer edge of the ring expands fairly rapidly to the periphery, while the inner margin contracts slowly toward the central field (producing "tunnel vision"). Long after the entire peripheral field is gone, a small oval of intact central field usually remains. Individuals with RP may qualify as legally blind by visual field criteria before visual acuity drops to the level established for legal blindness (20/200). Hence, visual field testing is useful not only for diagnosis, but also for establishing legal blindness.

- **Visual acuity (VA),** measured in individuals age five years and older using the Snellen charts, for assessment of distance vision (at 20') and macular (central) vision
- **Color vision,** which can be assessed subjectively by the affected individual or by objective testing

Electroretinography (ERG) determines objectively the functional status of the photoreceptors. ERG measures an electrical potential that arises in the retina after light stimulation and represents a composite response of millions of retinal cells. The measurement is made with a double electrode contact lens placed on the cornea, the output of which is amplified and displayed electronically. Responses obtained under dark-adapted conditions generally reflect rod function, and responses obtained under light-adapted conditions generally reflect cone function. Rod responses can be separated from cone responses, permitting definition of the type and extent of rod and/or cone involvement. Early and severe impairment of pure rod responses occurs in RP and is critical to the diagnosis of RP in young individuals. Individuals with advanced RP have nondetectable rod and cone responses.

Differential Diagnosis

It should be noted that individuals who present with initial symptoms of photopsia (sensation of lights flashing), abnormal central vision, abnormal color vision, or marked asymmetry in ocular involvement may not have RP, but another retinal degeneration or retinal disease. Some disorders to consider in the differential diagnosis of typical RP:

- **Usher syndrome.** The three types of Usher syndrome are inherited in an autosomal recessive manner. Individuals with Usher syndrome type 1 have congenital, profound, bilateral sensorineural hearing loss and no intelligible speech. All affected individuals have abnormalities of vestibular nerve function detected on caloric testing and associated mild, non-progressive ataxia. Symptoms of typical RP are usually noted in late childhood to early adolescence and are slowly progressive. Individuals with Usher syndrome type 2 have a mild-to-profound congenital sensorineural hearing impairment, normal vestibular responses, and late-adolescent-to-young-adult-onset RP. Individuals with Usher syndrome type 3 have bilateral progressive sensorineural hearing loss and RP.
- **Gyrate atrophy of the choroid and retina,** an autosomal recessive disorder, can be distinguished from RP by the appearance of the fundus and by appropriate laboratory tests. Early in the disease, circumscribed, discrete round patches of choroidal and retinal atrophy occur in the midperiphery. As the disease progresses these areas coalesce to form the sharply defined, scalloped defects of the pigment epithelium and choroid to which the term "gyrate" has been assigned. Ten- to 20-fold elevation of plasma ornithine concentration is caused by deficiency of the enzyme ornithine-ketoacid aminotransferase, which can be assayed in skin fibroblasts.
- **Choroideremia,** an X-linked disorder, can be distinguished by the fundus appearance. The early stage consists of fine pigmentary stippling and atrophy of the

posterior pole and mid-periphery of the fundus. In later stages, patchy retinal pigment epithelial and choroidal atrophy appear in the midperiphery and gradually coalesce into pale yellow confluent areas.

- **Cone-rod dystrophy,** sometimes called inverse or central RP, is characterized by bilateral and symmetric loss of cone function in the presence of reduced rod function. Like the term RP, the term "cone-rod dystrophy" refers to a group of disorders. In the cone-rod dystrophies, loss of central visual acuity, photoaversion, and color vision defects appear before peripheral visual loss and defective dark adaptation. Cone-rod dystrophies tend to have early onset. The fundus changes may be similar to those of RP. Cone-rod dystrophies are often syndromic; examples include Alström syndrome, Bardet-Beidl syndrome, and the neuronal ceroid lipofuscinoses.
- **Leber congenital amaurosis (LCA),** a severe dystrophy of the retina, typically becomes evident in the first year of life. Visual function is usually poor and accompanied by nystagmus, sluggish pupillary responses, photophobia, and hyperopia. The oculo-digital sign (repeated eye rubbing, poking, and pressing) is characteristic. The appearance of the fundus is extremely variable. While initially the retina may appear normal, a pigmentary retinopathy reminiscent of retinitis pigmentosa is frequently observed later in childhood. The electroretinogram (ERG) is characteristically "nondetectable" or severely subnormal.

  Seven genes are currently known to be associated with LCA: *CRX, CRB1, GUCY2D, AIPL1, RDH12, RPGRIP1*, and *RPE65*. Together these genes are estimated to account for, depending on the survey, from one-third to one-half of the cases of LCA. Two other disease loci for LCA have been reported. Most often, LCA is inherited in an autosomal recessive manner; rarely, it is inherited in an autosomal dominant manner as a result of mutations within the *CRX* gene.
- **Retinal-renal Senior Loken syndrome.** Ten percent of individuals with nephronophthisis, the most frequent genetic cause of chronic renal failure in children, have retinitis pigmentosa, constituting the renal-retinal Senior-Loken syndrome. Mutations in an evolutionarily conserved gene, *IQCB1* (also called *NPHP5*), is the most frequent cause of Senior-Loken syndrome [Otto et al 2005].
- **Mitochondrial disorders**. Mutations in mitochondrial DNA (mtDNA) cause a range of neurologic findings including dementia, stroke-like episodes, and peripheral neuropathy, as well as retinal dystrophy, Leber hereditary optic neuropathy, hearing loss, and diabetes mellitus. See *GeneReviews*: MELAS, MERRF, Mitochondrial DNA Deletion Syndromes, Mitochondrial Diseases Overview.
- **Unilateral RP.** Unilateral RP refers to unilateral functional and ophthalmoscopic changes, which are typical of RP resulting from a variety of causes, some of which may be genetic.
- **Treatable disorders.** It is important to note the three inherited disorders with retinal degeneration and systemic manifestations for which treatment exists: Bassen-Kornzweig disease (abetalipoproteinemia) with acanthocytosis and malabsorption; ataxia with vitamin E deficiency (AVED) (caused by mutations in *TTPA*, the gene encoding alpha-tocopherol transfer protein) with ataxia and neuropathy; and Refsum disease (phytanic acid oxidase deficiency) with neuropathy, ataxia, deafness, and cardiac arrhythmia.

Prevalence

The prevalence of RP is 19 to 27 per 100,000. The prevalence in the US and Europe is approximately 1/3,500 to 1/4,000. Haim (2002) reported that in Denmark the lifetime risk of developing RP is 1/2500. Similar frequencies are expected in other populations but have not been documented. RP shows no ethnic specificity, but RP caused by mutations in particular genes may be more frequent in certain isolated or consanguineous populations.

Causes

RP is classified as nonsyndromic, or "simple" (not affecting other organs or tissues); syndromic (affecting other systems such as hearing); or systemic (affecting multiple tissues). This overview focuses on nonsyndromic forms of RP. Nonsyndromic RP can be inherited in an autosomal dominant, autosomal recessive, or X-linked manner. Rare digenic forms also occur. Digenic RP occurs in individuals who are heterozygous for both a *ROM1* mutation and an *RDS* mutation.

Simplex cases (i.e., a single occurrence in a family) represent 10-40% of all individuals with RP and may result from a *de novo* autosomal dominant or X-linked mutation or autosomal recessive inheritance, or they may be individuals with relatives who are affected (perhaps mildly) but whose disease is not known to the affected individual.

Table 1 summarizes the relative proportion of probands with RP by mode of inheritance.

Table 1. Causes of Isolated Retinitis Pigmentosa by Mode of Inheritance

Mode of Inheritance	Proportion of All RP Probands
Autosomal dominant RP (adRP)	15-25%
Autosomal recessive RP (arRP)	5-20%
X-linked RP (xlRP)	5-15%
Unknown: Simplex	40-50%
Digenic RP	Very rare

Fishman 1978a

Gene mapping and gene discovery have revealed that the molecular genetic causes of RP are unusually complicated [Rivolta et al 2002]. Genes associated with RP encode proteins that are involved in phototransduction (the process by which the energy of a photon of light is converted in the photoreceptor cell outer segment into a neuronal signal), the visual cycle (production and recycling of the chromophore of rhodopsin), photoreceptor structure, and photoreceptor cell transcription factors [Phelan & Bok 2000]. However, the function of many genes associated with RP remains unknown.

The complexity is evident in genetic heterogeneity; that is, many different genes may cause the same disease [Hims et al 2003, Daiger 2004]. For most RP genes studied to date, many different disease-causing mutations have been identified, although in most cases a few specific mutations are "common" among affected individuals. In addition to the multiplicity of mutations, different mutations in the same gene may cause different diseases. For example, different mutations in *RHO*, the gene encoding rod opsin, may cause autosomal dominant RP, autosomal dominant congenital stationary night blindness, or, rarely, autosomal recessive RP. Mutations in *RDS,* the gene encoding peripherin, may cause autosomal dominant RP, autosomal dominant macular degeneration, or digenic RP. Clinical severity and disease phenotype often differ among individuals with the same mutation, most likely as the result of genetic and/or environmental factors.

These complexities are addressed in the following tables by listing some genes in more than one category and by indicating additional diseases that may by associated with specific genes.

Autosomal Dominant RP

Three genes, *RHO*, *RP1*, and *RDS*, account for approximately 25% to 30%, 5% to 10%, and 5% to 10% of adRP cases, respectively [Berson et al 2001, Sohocki et al 2001] (Table 2).

More than 100 *RHO* mutations have been reported but one, P23H, with distinct sectorial disease, is found in approximately 10% of Americans afffected with adRP.

RDS mutations are associated with clinical phenotypes ranging from RP to macular degeneration to complex maculopathies.

Of the *RP1* mutations known, two, Arg677stop and 2280del5, account for half of adRP cases caused by this gene.

Other cloned adRP genes, such as *PRPF31*, cause a substantial fraction of cases, but the specific prevalences are not yet known.

Table 2. Genes Causing Autosomal Dominant RP (adRP) (in Chromosomal Order)

Locus Name	Gene Symbol	Chromosomal Locus	Protein Name	Also Causes	Percent of adRP	OMIM
RP18	*PRPF3*	1q21.2	U4/U6 small nuclear ribonucleoprotein Prp3		Several families	OMIM OMIM
RP4	*RHO*	3q21-q24	Rhodopsin	Recessive RP; dominant CSNB [1]	25-30%	OMIM
RP7	*RDS*	6p21.1-cen	Peripherin	Dominant MD; digenic RP with *ROM1*; dominant adult vitelliform MD [2]	5-10%	OMIM
RP9	*RP9*	7p14.2	Retinitis pigmentosa 9 protein		Unknown	OMIM OMIM
RP10	*IMPDH1*	7q31.3-q32	Inosine 5'-monophosphate dehydrogenase 1		3-5%	OMIM OMIM
RP1	*RP1*	8q11-q13	Oxygen-regulated protein 1		5-10%	OMIM OMIM
	ROM1	11q13	Rod outer segment membrane protein 1	Digenic RP with *RDS*	Rare	OMIM
RP27	*NRL*	14q11.1-q11.2	Neural retina-specific leucine zipper protein	Autosomal recessive RP	Rare	OMIM
RP13	*PRPF8*	17p13.3	Pre-mRNA processing splicing factor 8		Unknown	OMIM
RP17	*CA4*	17q23	Carbonic anhydrase IV		Unknown	OMIM OMIM
RP30	*FSCN2*	17q25	Fascin 2		3% of Japanese with adRP	OMIM
	CRX	19q13.3	Cone-rod homeobox protein	Dominant CORD [3], dominant and recessive LCA [4]	Rare	OMIM OMIM
RP11	*PRPF31*	19q13.4	U4/U6 snRNP-associated 61-kD protein		15-20%	OMIM OMIM

Adapted from RetNet

1. CSNB= congenital stationary night blindness
2. MD= macular dystrophy
3. CORD= cone rod dystrophy
4. LCA= Leber congenital amaurosis

Autosomal Recessive RP

Most of the arRP genes are rare, causing 1% or fewer cases, but *RPE65* (expressed in the RPE), and *PDE6A* and *PDE6B* (phosphodiesterase subunits in the phototransduction cascade), cause 2-5% of cases; mutations in *USH2A*, which can also cause Usher syndrome, may account for up to 5% of arRP cases (Table 3). Mutations in a few genes are common causes of arRP in specific populations — such as *RP25* in Spain — but are rare elsewhere. The symptoms of these diseases may overlap with other autosomal recessive retinopathies. In particular, autosomal recessive, early-onset RP and Leber congenital amaurosis (LCA) are very similar.

Table 3. Genes Causing Autosomal Recessive RP (arRP) (in Chromosomal Order)

Locus Name	Gene Symbol	Chromosomal Locus	Protein Name	Also Causes	Percent of arRP	OMIM
RP20/LCA2	*RPE65*	1p31	Retinal pigment epithelium-specific 65-kD protein	LCA [1] (7-16%)	2%	OMIM OMIM
RP19	*ABCA4*	1p21-p13	Retinal-specific ATP-binding cassette transporter	Recessive Stargardt disease, and cone-rod dystrophy	~5% [2]	OMIM OMIM OMIM
RP12	*CRB1*	1q31-q32.1	Crumbs protein homolog 1	Recessive RP with para-arteriolar preservation of the RPE (PPRPE); LCA (9-13%)	Rare	OMIM OMIM
	USH2A	1q41	Usher syndrome type IIa protein	Usher syndrome, type 2	4-5%	OMIM
RP28		2p15-p11	Unknown		One family	OMIM
	MERTK	2q14.1	Proto-oncogene tyrosine-protein kinase MER tyrosine kinase		Rare	OMIM
RP26	*CERKL*	2q31.2-q32.3	Ceramide kinase-like protein		Rare	
	SAG	2q37.1	S-arrestin	Recessive Oguchi disease	Rare	OMIM OMIM
RP4	*RHO*	3q21-q24	Rhodopsin	Dominant RP; Dominant CSNB [3]	Rare	OMIM
CSNB3	*PDE6B*	4p16.3	Rod cGMP-specific 3', 5'-cyclic phosphodiesterase beta-subunit	Dominant CSNB	3-4%	OMIM OMIM
	CNGA1	4p12-cen	cGMP-gated cation channel alpha 1		Rare	OMIM
RP29		4q32-q34	Unknown		Rare; 4 families	
	LRAT	4q31	Lecithin retinol acyltransferase		Unknown	OMIM
	PDE6A	5q31.2-q34	Rod cGMP-specific 3', 5'-cyclic phosphodiesterase alpha-subunit		3-4%	OMIM
RP14	*TULP1*	6p21.3	Tubby-related protein 1		Rare	OMIM OMIM
RP25		6q14-q21	Unknown		10-20% of arRP in Spain	OMIM
	RGR	10q23	RPE-retinal G protein-coupled receptor	Dominant choroidal sclerosis	Unknown	OMIM
RP27	*NRL*	14q11.1-q11.2	Neural retina-specific leucine zipper protein	Dominant RP		
	NR2E3	15q23	Photoreceptor-specific nuclear receptor	Recessive enhanced S-cone syndrome	Rare; found in Sephardic Jews in Portugal	OMIM

	RLBP1	15q26	Cellular retinaldehyde-binding protein	Recessive Bothnia dystrophy; recessive retinitis punctata albescans; recessive Newfoundland rod-cone dystrophy	Unknown	OMIM
RP22		16p12.3-p12.1	Unknown		Rare	OMIM
	CNGB1	16q13	Cyclic-nucleotide-gated cation channel 4			OMIM

Adapted from RetNet

1. LCA= Leber congenital amaurosis
2. Klevering et al 2004
3. CSNB= congenital stationary night blindness

X-Linked RP

Mutations in *RPGR* (also called *RP3*) and *RP2* are the most common causes of xlRP (Table 4). Linkage studies suggest that they account for 70-90% and 10-20%, respectively, of X-linked RP. Earlier studies of *RPGR* failed to find mutations in a majority of families mapped to *RP3*; however, identification of an additional exon in *RPGR* (ORF15) has substantially increased the mutation detection rate [Bader et al 2003]. ORF15 is also the site of most or all dominant-acting mutations at this locus [Rozet et al 2002,Bader et al 2003,Sharon et al 2003].

In general, the multiple RP genes in close proximity to each other on the X chromosome make gene mapping and mutation detection difficult.

An important diagnostic complication is that carrier females may express mild retinal degeneration [Souied et al 1997, Grover et al 2000]. Therefore, families with X-linked inheritance of RP with affected females can be mistaken for families with adRP. Typically, though, retinal disease in affected females with X-linked RP is much less severe than that seen in males, in contrast to adRP, in which males and females are, on average, equally affected.

Table 4. Genes Causing X-Linked RP (xlRP) (in Chromosomal Order)

Locus Name	Gene Symbol	Chromosomal Locus	Protein Name	Also Causes	Percent of X-Linked RP	OMIM
RP23		Xp22	Unknown		Unknown	OMIM OMIM
RP6		Xp21.3-p21.2	Unknown		Unknown	OMIM
RP3	*RPGR*	Xp21.1	X-linked retinitis pigmentosa GTPase regulator	X-linked CSNB; X-linked cone dystrophy 1; X-linked atrophic MD, recessive; RP plus sensorineural hearing loss and recurrent sinopulmonary infection [1]	70% [2]	OMIM OMIM
RP2	*RP2*	Xp11.3	XRP2 protein	Peripapillary and macular atrophy [3]	8% [2]	OMIM
RP24		Xq26-q27	Unknown		Unknown	OMIM

Adapted from RetNet

1. Iannaccone, Breuer et al 2003; Iannaccone, Wang et al 2003; Koenekoop et al 2003; Zito et al 2003
2. Bader et al 2003, Sharon et al 2003
3. Dandekar et al 2004

Table 5. Mitochondrial Genes Causing Nonsyndromic RP

Gene Symbol	Locus	Prorein Name	Percent of RP	OMIM
MT-TS2	Mitochondrial DNA	Mitochondrial serine tRNA2	Rare	OMIM

Digenic RP

Digenic RP is caused by the simultaneous presence of a mutation in the *RDS* gene and a mutation in the *ROM1* gene [Dryja et al 1997]. In all cases reported, the same *RDS* mutation (L185P) was found, although three different *ROM1* mutations were identified in these families.

Abbreviations used in this section

RP	retinitis pigmentosa
adRP	autosomal dominant retinitis pigmentosa
arRP	autosomal recessive retinitis pigmentosa
RPE	retinal pigment epithelium
CSNB	congenital stationary night blindness
CORD	cone-rod dystrophy
LCA	Leber congenital amaurosis
MD	macular degeneration
xlRP	X-linked retinitis pigmentosa

Evaluation Strategy

Family history. A three-generation family history with attention to other relatives with possible RP should be obtained. Documentation of relevant findings in family members can be accomplished either through direct examination of those individuals or through review of their medical records including ERG testing, visual field testing, and ophthalmologic examination. Ophthalmologic evaluation of the mothers and daughters of males representing simplex cases may clarify the mode of inheritance in some families through detection of females who are carriers of X-linked RP. In rare cases, X-linked RP may be misdiagnosed as adRP on the basis of affected females and multiple affected generations; however, in such families, females with X-linked RP have less severe disease than males (and lack of male-to-male transmission supports X-linkage).

Physical evaluation. A medical history, ophthalmic history, and physical examination focusing on features associated with syndromic RP are necessary to establish the cause of retinitis pigmentosa in an affected individual.

Molecular genetic testing. Molecular genetic testing for mutations in some RP-causing genes is available in clinical laboratories (see Table 6). Molecular genetic testing for mutations in other RP-causing genes is available on a research basis only.

Table 6. Molecular Genetic Testing

Gene Symbol	Locus Name/Type	Inheritance	Test Availability
RP1	RP1	Autosomal dominant	Clinical Testing
RHO	RP4		Clinical Testing
RDS	RP7		Clinical Testing
PRPF8	RP13		Clinical Testing
PRPF3	RP18		Clinical Testing
CRB1	RP12	Autosomal recessive	Clinical Testing
ABCA4	RP19		Clinical Testing
RPE65	RP20		Clinical Testing
RLBP1	Bothnia type RP		Clinical Testing
RPGR	RP3	X-linked	Clinical Testing
RP2	RP2		

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, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Retinitis pigmentosa may be transmitted in an autosomal dominant, an autosomal recessive, or an X-linked recessive manner. Rare digenic forms also occur.

Risk to Family Members — Autosomal Dominant RP

Parents of a proband

- Most individuals diagnosed as having autosomal dominant retinitis pigmentosa will have an affected parent, although occasionally the family history will be negative.
- Family history may be "negative" because of early death of a parent, failure to recognize retinitis pigmentosa in family members, late onset in a parent, reduced penetrance of the mutant allele in an asymptomatic parent, or a *de novo* mutation for retinitis pigmentosa.

Sibs of a proband

- The risk to sibs depends upon the genetic status of the proband's parents.
- If one of the proband's parents has a mutant allele, the risk to the sibs of inheriting the mutant allele is 50%.

- Clinical severity and disease phenotype often differ among individuals with the same mutation; thus, age of onset and/or disease progression cannot be predicted.

Offspring of a proband

- Each child of an individual with autosomal dominant RP has a 50% chance of inheriting the mutation.
- Clinical severity and disease phenotype often differ among individuals with the same mutation; thus, age of onset and/or disease progression cannot be predicted.

Risk to Family Members — Autosomal Recessive RP

Parents of a proband

- The parents are obligate heterozygotes and, therefore, carry a single copy of a disease-causing mutation.
- Heterozygotes are asymptomatic.

Sibs of a proband

- At conception, each sib has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the chance of his/her being a carrier is 2/3.
- Heterozygotes are asymptomatic.
- Clinical severity and disease phenotype often differ among individuals with the same mutations; thus, age of onset and/or disease progression cannot be predicted.

Offspring of a proband. All offspring are obligate carriers.

Other family members of a proband. The sibs of obligate heterozygotes have a 50% chance of being heterozygotes.

Carrier Detection

Carrier testing for at-risk family members is available on a clinical basis for *RLBP1*, *CRB1*, *ABCA4*, and *RPE65* mutations once the disease-causing mutations have been identified in the proband.

Risk to Family Members — X-Linked Recessive RP

Parents of a proband

- Women who have an affected son and another affected male relative are obligate heterozygotes.
- If pedigree analysis reveals that an affected male represents a simplex case, several possibilities regarding his mother's carrier status need to be considered:

  1) He has a *de novo* disease-causing mutation and his mother is not a carrier.

  2) His mother has a *de novo* disease-causing mutation either a) as a "germline mutation" (i.e., occurring at the time of her conception and thus present in every cell of her body); or b) as "germline mosaicism" (i.e., present in her germ cells only).

3) His maternal grandmother has a *de novo* disease-causing mutation.

- No data are available, however, on the frequency of *de novo* gene mutations nor on the possibility or frequency of germline mosaicism in the mother as an etiology.

Sibs of a proband

- The risk to sibs depends upon the genetic status of the proband's mother.
- A female who is a carrier has a 50% chance of transmitting the disease-causing mutation with each pregnancy. Sons who inherit the mutation will be affected; daughters who inherit the mutation are carriers and may or may not have symptoms [Souied et al 1997].
- Clinical severity and disease phenotype often differ among individuals with the same mutation; thus, age of onset and/or disease progression cannot be predicted.

Offspring of a proband. All the daughters of an affected male are carriers; none of his sons will be affected.

Other family members of a proband. The proband's maternal aunts and their offspring may be at risk of being carriers or being affected (depending upon their gender, family relationship, and the carrier status of the proband's mother).

Risk to Family Members — Digenic Inheritance

Digenic RP is caused by the simultaneous presence of mutations in the *RDS* gene and the *ROM1* gene [Dryja et al 1997].

Parents of a proband

- The parents are obligate heterozygotes; one parent carries an *RDS* mutation and the other parent carries an *ROM1* mutation.
- Heterozygotes are asymptomatic.

Sibs of a proband

- At conception, each sib has a 25% chance of having RP, a 25% chance of being an asymptomatic carrier of the *RDS* mutation, a 25% chance of being an asymptomatic carrier of the *ROM1* mutation, and a 25% chance of being unaffected and not a carrier of either mutation.
- Once an at-risk sib is known to be hearing, the chance of his/her being a carrier is 2/3.
- Heterozygotes are asymptomatic.

Offspring of a proband. All offspring are carriers of either the *RDS* mutation or the *ROM1* mutation.

Other family members of a proband. Each sib of an obligate heterozygote is at a 50% risk of being heterozygous.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration

should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which molecular genetic testing is available on a research basis only, or in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

No laboratories offering molecular genetic testing for prenatal diagnosis of RP are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which a/the disease-causing mutation(s) has/have been identified in an affected family member in a research or clinical laboratory. For laboratories offering custom prenatal testing, see f Testing.

Preimplantation genetic diagnosis (PGD). Preimplantation genetic diagnosis may be available for families in which a/the disease-causing mutation(s) has/have been identified in an affected family member in a research or clinical laboratory. For laboratories offering PGD, see Testing.

Management

Treatment of Manifestations

Retinal degeneration. Therapy with 15,000 IU per day of vitamin A palmitate has a possible slowing effect on changes in retinal function detected by ERG [Berson et al 1993, Massof & Finkelstein 1993]. Of note, the *only* preparation tested has been vitamin A palmitate. Vitamin A palmitate therapy is not recommended for those under age 18 years. Although toxicity with long-term use has not been noted [Sibulesky et al 1999], routine monitoring of serum vitamin A concentration and liver function has been recommended for any individual on vitamin A palmitate therapy. Women of childbearing age need to be cautioned about potential teratogenic effects of high-dose vitamin A.

Cystoid macular edema. Some therapeutic success has been reported with diamox therapy.

Cataracts. Most affected individuals with a visual field of greater than 10° are not incapacitated by posterior subcapsular cataracts. Those with a visual field of less than 10° usually report significant improvement in visual function following lens extraction [Jackson et al 2001].

Optical aids. Use of CPF 550 lenses (Corning Photochromatic Filter manufactured by Corning Glass Works), which filter out 97-99% of the spectral and ultraviolet energy below 550 nm wavelength, has been promoted for individuals with RP to increase eye comfort by reducing glare and internal light scatter, to improve contrast, and to reduce adaptation time from light to dark and vice versa.

Various optical aids have been proposed for individuals with peripheral visual loss and preserved central vision, although all have drawbacks.

Low vision aids such as magnifiers and closed circuit television may provide useful reading vision for individuals with reduced central acuity and constricted visual fields.

Wide-field, high-intensity flashlights produce a bright wide beam of light and improve the nighttime mobility of individuals with RP. They are inexpensive and allow binocular viewing, but are large, heavy, and conspicuous.

Agencies for the visually impaired. In the US, publicly funded agencies at the state level provide services for the blind or those with progressive eye disorders; services include vocational training, mobility training, and skills for independent living.

Agents/Circumstances to Avoid

Vitamin E. Because vitamin E may adversely affect the course of RP, it is recommended that individuals with RP avoid high-dose supplements (e.g., 400 IU/d) [Berson 2000].

Therapies Under Investigation

Lutein. One study [Aleman et al 2001] of oral supplementation with 20 mg/d lutein for six months demonstrated increased macular pigment in approximately 50% of individuals with RP or Usher syndrome but no change in central vision. The long-term effects of such supplementation are unknown.

UV-A and UV-B blocking sunglasses have been recommended based on animal studies.

Gene therapy. Hypothetical approaches to gene therapy have been discussed [Dejneka & Bennett 2001, Farrar et al 2002, Delyfer et al 2004].

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Docosahexaenoic acid therapy (1200 mg/d) plus vitamin A palmitate showed no effect on disease course in several studies [Berson et al 2004a, Berson et al 2004b, Hoffman et al 2004].

Prolonged light deprivation has not been demonstrated to be effective in altering the progression of RP.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select*  *for the most up-to-date Resources information.*—ED.

Retinitis Pigmentosa International
PO Box 900
Woodland Hills, CA 91365
Phone: 818-992-0500
Fax: 818-992-3265

Email: info@rpinternational.org
www.rpinternational.org

American Council of the Blind (ACB)
1155 15th Street NW, Suite 1004
Washington, DC 20005
Phone: 800-424-8666; 202-467-5081
Fax: 202-467-5085
Email: info@acb.org
www.acb.org

Foundation Fighting Blindness
11435 Cronhill Drive
Owings Mill, MD 21117-2220
Phone: 888-394-3937 (toll-free); 800-683-5555 (toll-free TDD); 410-568-0150 (local)
Email: info@blindness.org
www.blindness.org

National Federation of the Blind (NFB)
1800 Johnson Street
Baltimore, MD 21230
Phone: 410-659-9314
Fax: 410-685-5653
Email: nfb@nfb.org
www.nfb.org

Retina International
Ausstellungsstrasse 36
CH-8005 Zurich
Switzerland
Phone: 011-41-1-444-10-7
Fax: 011-41-1-444-10-7
Email: info@rpinternational.org
www.retina-international.org

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Revision History

- 16 September 2005 (me) Comprehensive update posted to live Web site
- 21 October 2004 (bp) Revision: *PRPF3* added
- 7 July 2004 (bp) Revision: Table 6; change in test availability
- 19 April 2004 (bp) Revision: Clinical testing for *PRPF8* available
- 23 June 2003 (me) Comprehensive update posted to live Web site
- 4 August 2000 (bp, me) Overview posted to live Web site

- November 1997 (bp, sd) First draft