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Nonsyndromic Retinitis Pigmentosa Overview

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Summary

The goals of this overview on nonsyndromic retinitis pigmentosa are the following.

Goal 1

Describe the clinical characteristics of nonsyndromic retinitis pigmentosa.

Goal 2

Review the causes of nonsyndromic retinitis pigmentosa.

Goal 3

Provide an evaluation strategy to identify the genetic cause of nonsyndromic retinitis pigmentosa in a proband.

Goal 4

Provide a brief summary of management of nonsyndromic retinitis pigmentosa.

Goal 5

Inform genetic risk assessment of family members of a proband with nonsyndromic retinitis pigmentosa.

1. Clinical Characteristics of Nonsyndromic Retinitis Pigmentosa

Retinitis pigmentosa (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. RP is classified as nonsyndromic, or "simple" (not

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affecting other organs or tissues); syndromic (affecting other neurosensory systems such as hearing); or systemic (affecting multiple tissues). This overview focuses on nonsyndromic forms of RP.

Clinical Manifestations of Retinitis Pigmentosa

Night blindness. In RP, loss of rod function predominates early in the clinical course. The initial symptom of RP is usually defective dark adaptation (i.e., nyctalopia 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 misconstrued as "clumsy" before constriction of visual fields (i.e., "tunnel vision") is detected.

Visual acuity. Sensitive tests of cone function can document early cone involvement; however, 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]. Central acuity loss can occur at all ages from cystoid macular edema (CME), which is estimated to occur in approximately 10%-50% of individuals with RP, depending on the study, the genetic type, and the diagnostic tool. Estimates of CME incidence have been higher when optical coherence tomography (OCT) is used rather than fluorescein angiography (FA), which may not demonstrate leakage in affected individuals [Hajali et al 2008].

Some investigators have found a general correlation between age-related visual acuity and mode of inheritance. Fishman [1978] found that individuals with autosomal dominant RP had the best prognosis, with a visual acuity of 20/30 or better in the majority of individuals younger than age 30 years. Males with X-linked RP had the worst prognosis, with a visual acuity worse than 20/200 in all individuals older than age 50 years. Individuals with autosomal recessive and simplex RP (i.e., a single occurrence in the family) were intermediate in severity.

Fundus appearance. 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.

Moderate to severe 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 cause of disease.

Posterior subcapsular cataracts characterized by yellowish crystalline changes in the visual axis of the posterior 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. Approximately half of individuals with RP eventually require (and usually benefit from) cataract surgery.

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 occur frequently in RP, may be associated with arcuate visual field loss, and are not diagnostic of a specific subtype.

Exudative vasculopathy, often called Coats-like disease, is the rare occurrence in individuals with severe or advanced RP of telangiectatic vessels, lipid deposition in the retina, and serous retinal detachment [Khan et al 1988]. The cause of exudative vasculopathy in RP is unknown. However, pathogenic variants in *CRB1*, a cause of Leber congenital amaurosis and autosomal recessive RP, have been associated with Coats-like exudative vasculopathy [den Hollander et al 2001]. When seen in children or young adults, Coats-like vascular changes should be monitored for progression and may require treatment.

Sector RP is a term that has been used to describe changes in one quadrant or one half of each fundus. Most commonly, the inferior and nasal 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 may lack symptoms of defective dark adaptation, although widespread abnormalities of rod and cone function are usually detected by ERG. The incidence of true sector RP is infrequent: many forms of RP can present initially with a sectorial distribution that, when followed over decades, develops into a widespread, diffuse disease.

Sectoral changes have been observed in autosomal dominant RP (e.g., in people with the common *RHO* p.Pro23His pathogenic variant) and in females heterozygous for X-linked RP.

The low incidence of sector RP may indicate its rarity, or may reflect the fact that the mildness of symptoms results in infrequent diagnosis.

RP during pregnancy. Five to ten percent of women with RP report decreased vision during pregnancy that frequently did not recover post partum; however, no objective data are available [Heckenlively et al 1988, Sunness 1988].

Physiologic changes during pregnancy, such as increased thickness and curvature of the cornea and changes in the accommodative power of the lens, can alter a woman's refractive state.

Pregnant women are at increased risk for central serous retinopathy, progression of preexisting diabetic retinopathy, and other conditions that can affect vision.

Some woman with poor nutritional intake may be at increased risk for vitamin A deficiency and nyctalopia during pregnancy (for review see Garg & Aggarwal [2012]).

Establishing the Clinical Diagnosis of Retinitis Pigmentosa

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

- Rod dysfunction as measured by one of the following:
  - Dark adaptation (elevated rod final threshold)
  - Electroretinogram (ERG) (nondetectable or severely reduced rod responses, with prolonged implicit time, often with lesser reduction and prolongation of cone-mediated responses)
- Progressive loss in photoreceptor function
- Loss of peripheral vision that often is greater superiorly but can involve other regions as well
- Bilateral involvement that has a high degree of symmetry, with respect to both the severity and the pattern of visual field loss and retinal changes

The American Academy of Ophthalmology (AAO) Recommendations on Clinical Assessment of Patients with Inherited Retinal Degenerations [Duncan et al 2016] include the following assessments:

- Ocular and medical history
- Pedigree detailing the family history of eye disease
- Clinical eye examination
  - Best corrected visual acuity (BCVA)
  - Slit lamp biomicroscopy
  - Intraocular pressure
  - Indirect ophthalmoscopy
- Imaging
  - Color fundus photos
  - Fundus autofluorescence (reduced illumination when possible)
  - Spectral domain optical coherence tomography (sdOCT)
- Visual fields
- Full-field electroretinography (ffERG)
- Molecular genetic testing (See Evaluation Strategy to Identify the Genetic Cause of Nonsyndromic Retinitis Pigmentosa.)

Best corrected visual acuity (BCVA) is measured in individuals age five years and older using the Snellen charts, for assessment of macular (central) vision both at distance (20') and at near (14").

Indirect 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 long-standing 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.

Spectral domain optical coherence tomography (sdOCT) captures micron-resolution cross-sectional images of the retina, most typically of the macular region. It can be used to demonstrate which outer layers are involved in the retinal degeneration, measure retinal thickness, and help with the diagnosis and follow up of cystoid macular edema [Hajali et al 2008, Hood et al 2009].

Recent advances in **adaptive optics** allow highly detailed imaging of the retina with a resolution of two microns, potentially allowing clinicians and investigators to follow photoreceptor degeneration in individuals with RP at the cellular level. However, this technology is not in widespread clinical use (for review, see Carroll et al [2013]).

Visual field testing (also called perimetry) is the mapping of subjectively perceived test objects, which are ellipses of light varying in brightness and in size from 1/16 mm to 64 mm, projected on a uniformly illuminated background. Symptomatic defective dark adaptation in individuals with RP is usually accompanied by peripheral visual field defects or mid-peripheral scotomas (blind spots). In early RP, a ring scotoma often is present in the mid-periphery of the visual field approximately 20-25 degrees from fixation. As the RP progresses, the outer edge of the ring expands toward the periphery, while the inner margin contracts slowly toward the central field (producing "tunnel vision"). Islands of vision may persist for years in the far periphery, most often temporally and inferiorly. Long after the entire peripheral field is gone, a small oval of intact central field typically remains. Individuals with RP may qualify as legally blind by visual field criteria (horizontal diameter of field 20 degrees or less to a size III4e test target in the better eye) 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 staging of the disease, for qualifying affected individuals to drive, for assessment of disability, and for establishing legal blindness.

The electroretinogram (ERG) is an objective test of the functional status of the photoreceptors and neuronal layers of the retina. The ERG measures an electrical potential that originates in the outer segments of the photoreceptors in the retina after light stimulation and represents a composite response of millions of retinal cells. The measurement is made with a contact lens electrode placed on the cornea, the output of which is amplified electronically and recorded. Responses obtained under dark-adapted conditions with stimuli that are dim or blue generally reflect rod function, and responses obtained under light-adapted conditions or with 30 Hz flicker stimuli 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 isolated rod responses is a characteristic feature in RP and its documentation is important to the diagnosis in young individuals. Greater cone loss than rod loss is typical for cone-rod degenerations but uncommonly can occur in otherwise typical RP. In more severe or advanced forms of RP, cone loss occurs and eventually the ERG is nondetectable above noise.

The full-field ERG (ffERG) stimulates and records responses from the entire retina and has traditionally been used to follow disease progression in people with retinitis pigmentosa.

The multifocal ERG (mfERG) stimulates the central retina only and, thus, can record local responses across the macula. The mfERG can detect residual macular function in individuals with advanced disease from RP and – in conjunction with the ffERG – distinguish cone-rod degeneration from rod-cone degeneration. Therefore, it is useful in long-term follow up as well as monitoring of visual function in clinical trials involving advanced RP [Hood et al 2003, Nagy et al 2008].

Differential Diagnosis of Nonsyndromic Retinitis Pigmentosa

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 retinitis pigmentosa (RP) are listed below. In many instances, they are caused by pathogenic variants in the same genes implicated in RP.

Usher syndrome. The three types of Usher syndrome are inherited in an autosomal recessive manner.

- Usher syndrome type I. Congenital, profound, bilateral sensorineural hearing loss and lack of development of speech. All affected individuals have abnormalities of vestibular nerve function detected on caloric testing with associated gait imbalance. Symptoms of typical RP are usually noted in late childhood to early adolescence and are slowly progressive.
- Usher syndrome type II. Mild-to-profound congenital sensorineural hearing impairment, normal vestibular responses, and late-adolescent-to-young-adult-onset RP
- Usher syndrome type III. Bilateral variable sensorineural hearing loss, vestibular dysfunction, and RP – all of which are slowly progressive

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 [Hayasaka et al 1985]. Early in the disease, circumscribed, discrete round patches of choroidal and retinal atrophy occur in the mid-periphery. 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 mid-periphery and gradually coalesce.

Cone or cone-rod dystrophy, sometimes called inverse or central RP, refers to a group of disorders characterized by bilateral and symmetric loss of cone function in the presence of reduced rod function. Loss of central visual acuity, photoaversion, and color vision defects appear before peripheral visual loss and defective dark adaptation. The fundus changes may be similar to those of RP. Cone-rod dystrophies tend to demonstrate early onset and are often syndromic; examples include Alström syndrome, Bardet-Biedl syndrome, the neuronal ceroid lipofuscinoses, and Joubert syndrome and related disorders (JSRD). Note that the "oculorenal" phenotype is included in the spectrum of JSRD, which encompasses Senior-Løken syndrome (retinopathy and juvenile-onset nephronophthisis) and Dekaban-Arima syndrome (retinopathy and cystic dysplastic kidneys).

Leber congenital amaurosis (LCA), a severe dystrophy of the retina, typically becomes evident in the first year of life. Most forms are autosomal recessive. 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 to elicit retinal stimulation) 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.

Congenital disorders of glycosylation (CDG) type 1a. The congenital disorders of glycosylation encompass several multisystem syndromic disorders caused by defective protein glycosylation. Affected individuals present with developmental delay, dysmorphic features, and neurologic findings. CDG 1a, the most common and well-characterized subtype, includes ophthalmologic findings (e.g., strabismus, progressive myopia, and retinal degeneration) in 50%-70% of cases [de Lonlay et al 2001]. Individuals may display attenuated retinal vessels, pallor of the optic disc, restricted visual fields, and diminished rod function on ERG [Jensen et al 2003, Morava et al 2009]. (See also Congenital Disorders of Glycosylation Overview.)

Mitochondrial disorders. Pathogenic variants 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 [Fraser et al 2010]. See MELAS, MERRF, Mitochondrial DNA Deletion Syndromes, and Mitochondrial Diseases Overview.

Unilateral RP refers to unilateral functional and ophthalmoscopic changes; the underlying etiology and mechanism remain unknown. Many non-genetic causes of retinopathy may masquerade as unilateral RP and should be excluded (see Non-Inherited Retinopathies). Although some have proposed skewed X-chromosome inactivation in female carriers of X-linked RP as one mechanism of unilateral RP, to date there have been no published reports of unilateral X-linked RP and most cases of unilateral RP are either simplex or autosomal dominant [Farrell 2009]. Typically other affected family members have bilateral RP, indicating that unilateral involvement itself is not necessarily heritable.

Treatable Disorders

It is important to note the three inherited disorders with retinal degeneration and systemic manifestations for which treatment exists.

- Abetalipoproteinemia (Bassen-Kornzweig disease) presents with acanthocytosis and malabsorption, and is treated with vitamins A and E.
- Ataxia with vitamin E deficiency (AVED) with ataxia and neuropathy is caused by biallelic pathogenic variants in *TTPA*, encoding alpha-tocopherol transfer protein, and is treated with vitamin E.

- Refsum disease (phytanic acid oxidase deficiency) presents with neuropathy, ataxia, deafness, and cardiac arrhythmia, and is treated with dietary reduction of phytanic acid.

Non-Inherited Retinopathies

Many non-inherited causes of retinal inflammation can present with fundus findings similar to retinitis pigmentosa, including trauma, infection, autoimmune retinopathy, and drug toxicity [Hamel 2006].

Prevalence of Retinitis Pigmentosa

The prevalence of RP is 1:3,000 to 1:7,000 persons, or 14 to 33 per 100,000 [Haim 2002]. 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 1:2,500. Similar frequencies are expected in other populations but have not been documented.

RP shows no ethnic predilection; however, the spectrum of pathogenic variants within a given RP-associated gene may vary between populations. This is especially true for certain isolated populations or those with a high rate of consanguinity. Furthermore, the frequency of a specific dominant or recessive pathogenic variant may be common in a particular population as a result of a founder effect or may change due to genetic drift. For example, the *RHO* pathogenic variant NM_000539.3:c.68C>A (NP_000530.1:p.Pro23His), which accounts for 12%-14% of all adRP in Americans of European origin, is otherwise rare [Sullivan et al 2006] (see Table 2).

2. Causes of Nonsyndromic Retinitis Pigmentosa

Gene mapping and gene discovery have revealed unusually complicated molecular genetic causes of RP [Daiger et al 2013]. Many of the 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, or photoreceptor gene transcription [Berger et al 2010, Wright et al 2010]. However, the function of many genes in which pathogenic variants cause RP remains unknown.

The complexity of RP is evident:

- **Locus heterogeneity.** Pathogenic variants in many different genes cause the same phenotype [Daiger et al 2007].
- **Allelic heterogeneity.** Many different pathogenic variants occur within the same gene; however, a few specific pathogenic variants may be "common" among affected individuals.
- **Allelic disorders.** Different pathogenic variants in the same gene may cause different phenotypes. For example, different pathogenic variants in *RHO*, the gene encoding rhodopsin, may cause autosomal dominant RP, autosomal dominant congenital stationary night blindness, or, rarely, autosomal recessive RP. Pathogenic variants in *PRPH2* (previously known as *RDS*), the gene encoding peripherin, may cause autosomal dominant RP, autosomal dominant macular degeneration, or, with a pathogenic variant in *ROM1*, digenic RP.
- **Clinical severity and disease phenotype** often differ among individuals with the same pathogenic variant, most likely as the result of genetic and/or environmental modifying factors.

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* pathogenic variant and a *PRPH2* pathogenic variant [Kajiwara et al 1994].

The likelihood of finding the underlying pathogenic variant(s) in an individual with RP depends on the type of disease, mode of inheritance, and testing methods used. In general, reported success rates using multigene panels, next-generation sequencing, or exome sequencing range from 50% to 80% [Audo et al 2012, Neveling et al 2012, O'Sullivan et al 2012, Corton et al 2013, Wang et al 2014, Xu et al 2014].

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

Table 1. Causes of Nonsyndromic 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 [1]	40%-50%
Digenic RP	Very rare

Daiger et al [2007]
1. Simplex refers to a single reported occurrence of RP in a family.

Nonsyndromic Autosomal Dominant RP

Table 2. Genes Associated with Nonsyndromic Autosomal Dominant Retinitis Pigmentosa (adRP)

Gene	Frequency [1, 2]	OMIM Phenotype Description [1]	Links to RetNet Database [2]
ARL3	Rare	604695	RetNet
BEST1	Rare	613194	RetNet
CA4	Rare	600852	RetNet
CRX	1% of persons with adRP	602225	RetNet
FSCN2	Unlikely cause of disease [3]	607921	RetNet
GUCA1B	5% in Japan; rare in UK	613827	RetNet
HK1	Rare	142600	RetNet
IMPDH1	2%-3%	180105	RetNet
KLHL7	1%-2%	612943	RetNet
NR2E3	1%-2%	611131	RetNet
NRL	Rare	613750	RetNet
PRPF3	1%	601414	RetNet
PRPF6	Rare	613983	RetNet
PRPF8	2%-3%	600059	RetNet
PRPF31 [4]	8% of adRP; 2.5% of adRP is caused by *PRPF31* genomic rearrangements detected by deletion/duplication analysis, not sequence analysis	600138	RetNet
PRPH2	5%-10% (Note: Phenotypes range from macular degeneration to complex maculopathies.)	608133	RetNet
RDH12	Unknown	608830	RetNet
RHO	20%-30% (Note: The variant NM_000539.3:c.68C>A [NP_000530.1:p.Pro23His], associated with distinct sectorial disease, is found in ~12%-14% of Americans of European origin with adRP. [5])	613731	RetNet
ROM1	Rare	608133	RetNet
RP1	3%-4%	180100	RetNet

Table 2. continued from previous page.

Gene	Frequency [1, 2]	OMIM Phenotype Description [1]	Links to RetNet Database [2]
RP9 (formerly *PAP1*)	Rare; candidate gene, *PAP1*, is not supported by subsequent studies. [3]	180104	RetNet
RPE65	Rare	613794	RetNet
SEMA4A	3%-4% in Pakistan	610282	RetNet
SNRNP200	1%-2%	610359	RetNet
SPP2	Rare	602637	RetNet
TOPORS	1%	609923	RetNet

Information is presented alphabetically by gene.
Data are compiled from the following standard references: gene from HGNC; OMIM numbers from OMIM; protein from UniProt. See RetNet for mapped loci for which no gene has yet been identified.
See Retinitis Pigmentosa: Phenotypic Series to view genes associated with this phenotype in OMIM.
1. OMIM gene description is provided if an OMIM retinitis pigmentosa phenotype description is not available.
2. For additional information including allelic disorders (i.e., other phenotypes associated with a pathogenic variant in a given gene) see RetNet.
3. Daiger et al [2008]
4. Noncoding variants have been identified that would not be detected by exome sequencing [Daich Varela et al 2023].
5. Sullivan et al [2006]

Nonsyndromic Autosomal Recessive RP

Table 3. Genes Associated with Nonsyndromic Autosomal Recessive Retinitis Pigmentosa (arRP)

Gene	Frequency [1, 2]	OMIM Phenotype Description [1]	Links to RetNet Database [2]
ABCA4	2%-5%	601718	RetNet
ADGRA3	Rare	612303	RetNet
AGBL5	Rare	617023	RetNet
ARL6	Rare	613575	RetNet
ARL2BP	Rare	615434	RetNet
BBS1	≤1%	209901	RetNet
BBS2	≤1%	616562	RetNet
BEST1	≤1%	613194	RetNet
PCARE (*C2orf71*)	≤1%	613428	RetNet
CFAP418 (*C8orf37*)	≤1%	614500	RetNet
CERKL	3%-4% in Spain	608380	RetNet
CLRN1	≤1%	614180	RetNet
CNGA1	1%-2%	613756	RetNet
CNGB1	≤1%	613767	RetNet
CRB1 [3]	6%-7% in Spain	600105	RetNet
CYP4V2	≤1%	608614	RetNet
DHDDS	≤1%	613861	RetNet
DHX38	≤1%	605584	RetNet

Table 3. continued from previous page.

Gene	Frequency [1, 2]	OMIM Phenotype Description [1]	Links to RetNet Database [2]
EMC1	≤1%	616846	RetNet
EYS	10%-30% in Spain; common in China	602772	RetNet
FAM161A	≤1%	606068	RetNet
HGSNAT	≤1%	616544	RetNet
IDH3B	≤1%	612572	RetNet
IFT140 [3]	≤1%	617781	RetNet
IFT172	≤1%	616394	RetNet
IMPG2	≤1%	613581	RetNet
KIAA1549	Rare	613344	RetNet
KIZ	Rare	615780	RetNet
LRAT	≤1%	613341	RetNet
MAK	≤1%	614181	RetNet
MERTK	≤1%	613862	RetNet
MVK	Rare	251170	RetNet
NEK2	Rare	615565	RetNet
NEUROD1	Rare	601724	RetNet
NR2E3	Rare; found in Sephardic Jews in Portugal	611131	RetNet
NRL	≤1%	613750	RetNet
PDE6A	2%-5%	180071	RetNet
PDE6B	2%-5%	613801	RetNet
PDE6G	≤1%	613582	RetNet
POMGNT1	Rare	617123	RetNet
PRCD	≤1%	610599	RetNet
PROM1	≤1%	612095	RetNet
RBP3	≤1%	615233	RetNet
RGR	≤1%	613769	RetNet
RHO	≤1%	613731	RetNet
RLBP1	≤1%	180090	RetNet
RP1	≤1%	180100	RetNet
RPE65	2%-5%	613794	RetNet
SAG	2%-3% in Japan	613758	RetNet
SPATA7	≤1%	604232	RetNet
SLC7A14	Rare	615725	RetNet
TRNT1	Rare	612907	RetNet
TTC8	≤1%	613464	RetNet

Table 3. continued from previous page.

Gene	Frequency [1, 2]	OMIM Phenotype Description [1]	Links to RetNet Database [2]
TULP1	≤1%	600132	RetNet
USH2A [3]	10%-15% (Note: Also causes Usher syndrome type II.)	613809	RetNet
ZNF408	≤1%	616469	RetNet
ZNF513	≤1%	613617	RetNet

Information is presented alphabetically by gene.
Data are compiled from the following standard references: gene from HGNC; OMIM numbers from OMIM; protein from UniProt. See RetNet for mapped loci for which no gene has yet been identified.
See Retinitis Pigmentosa: Phenotypic Series to view genes associated with this phenotype in OMIM.
1. OMIM gene description is provided if an OMIM retinitis pigmentosa phenotype description is not available.
2. For additional information including allelic disorders (i.e., other phenotypes associated with a pathogenic variant in a given gene) see RetNet.
3. Noncoding variants have been identified that would not be detected by exome sequencing [Daich Varela et al 2023].

The symptoms of nonsyndromic autosomal recessive RP may overlap with other autosomal recessive retinopathies, in particular, autosomal recessive early-onset RP and Leber congenital amaurosis (LCA) (see Differential Diagnosis).

Nonsyndromic X-Linked RP

Table 4. Genes Associated with Nonsyndromic X-Linked RP (xlRP)

Gene	Frequency [1, 2]	OMIM Phenotype Description [1]	Links to RetNet Database [2]
OFD1	Rare	300424	RetNet
RP2	10%-20%	312600	RetNet
RPGR	70%-90% [3]	300029	RetNet

Information is presented alphabetically by gene.
Data are compiled from the following standard references: gene from HGNC; OMIM numbers from OMIM; protein from UniProt. See RetNet for mapped loci for which no gene has yet been identified.
See Retinitis Pigmentosa: Phenotypic Series to view genes associated with this phenotype in OMIM.
1. OMIM gene description is provided if an OMIM retinitis pigmentosa phenotype description is not available.
2. For additional information including allelic disorders (i.e., other phenotypes associated with mutation in a given gene) see RetNet.
3. Pathogenic variants in *RPGR* (also called *RP3*) and *RP2* are the most common causes of xlRP. Linkage studies suggest that they account for 70%-90% and 10%-20% of xlRP, respectively [Vervoort et al 2000]. Note: Earlier studies of *RPGR* failed to find a pathogenic variant in a majority of families that mapped to *RP3*; however, identification of an additional exon in *RPGR* (ORF15) substantially increased the detection rate [Bader et al 2003]. ORF15 is the site of many of the pathogenic variants at this locus [Mears et al 2000, Rozet et al 2002, Sharon et al 2003].

Of note, 15% of males with RP who are simplex cases (i.e., a single occurrence of RP in a family) have an *RPGR* pathogenic variant [Branham et al 2012].

Retinal disease in females with xlRP is typically less severe than that seen in males; in contrast, in adRP males and females are, on average, equally affected. Because females heterozygous for a pathogenic variant in an X-linked RP-related gene may be unaffected or express mild to severe retinal degeneration [Souied et al 1997, Grover et al 2000], families with xlRP in which some females are affected can be mistaken for families with adRP. For example, in a cohort of 258 families with apparent adRP, 19 families (7.4%) had xlRP caused by pathogenic variants in *RPGR* and two (0.8%) had xIRP caused by pathogenic variants in *RP2* [Churchill et al 2013]. Nonetheless, this observation likely underestimates the actual frequency of *RPGR*-related RP in pedigrees consistent with adRP.

Digenic RP

Digenic RP is caused by the simultaneous presence of a pathogenic variant in *PRPH2* and a pathogenic variant in *ROM1* [Dryja et al 1997]. The same *PRPH2* pathogenic variant (NM_000322.4:c.554T>C; NP_000313.2:p.Leu185Pro) was found in all cases reported; three different *ROM1* pathogenic variants were identified in these families. In a cohort of 215 families with apparent adRP, one family (0.5%) had digenic RP [Daiger et al 2008].

3. Evaluation Strategy to Identify the Genetic Cause of Nonsyndromic Retinitis Pigmentosa in a Proband

The diagnosis of nonsyndromic retinitis pigmentosa **is established** in a proband by identification of pathogenic variant(s) in a given gene (see Table 1, Table 2, and Table 3).

The recommendations of the American Academy of Ophthalmology (AAO) task force on genetic testing of inherited eye diseases:

- Offer genetic testing to individuals with clinical findings suggestive of a Mendelian disorder the genetic cause(s) of which have been identified;
- Use a Clinical Laboratories Improvement Amendments (CLIA)-certified lab;
- Provide a copy of the genetic test report to the individual and avoid direct-to-consumer genetic testing [Stone et al 2012].

Molecular genetic testing approaches can include a combination of **targeted gene testing** (multigene panel, single-gene testing) or **genomic testing** (comprehensive genomic sequencing) [Stone et al 2012].

Targeted-gene testing requires the clinician to determine which gene(s) are likely involved, whereas genomic testing may not. Because the causes of nonsyndromic RP cannot in general be distinguished by clinical findings or family history, most individuals with nonsyndromic RP are diagnosed by use of the recommended testing or testing to consider.

Recommended Testing

A multigene RP panel that includes many of the RP-associated genes of interest (see Table 2, Table 3, and Table 4) is currently the most effective approach to testing. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Single-gene testing. Single-gene testing has a limited role in determining the genetic cause of nonsyndromic RP. Two exceptions are:

- *RPGR*-related RP, which accounts for 80% of X-linked RP (Table 4) and is thus appropriate to consider as a recommended test for an affected individual from a family with nonsyndromic X-linked RP. Single-gene

testing in this instance may be more efficient and cost effective than a multigene RP panel. Note: Some clinically relevant regions of *RPGR*, such as ORF15, are technically difficult to interrogate with next-generation sequencing and therefore may not be included in multigene panel testing [Churchill et al 2013].

- In any family with a *PRPH2* pathogenic variant or a *ROM1* pathogenic variant (Table 2) in which inheritance appears to be non-Mendelian, digenic inheritance should be considered and testing for a pathogenic variant in the other gene performed.

Testing to Consider

Comprehensive genomic testing (when available) including exome sequencing and genome sequencing may be considered if the phenotype alone is insufficient to support gene-targeted testing. For additional issues regarding the use of comprehensive genomic sequencing see the American Academy of Ophthalmology (AAO) task force on genetic testing of inherited eye diseases [Stone et al 2012].

Note: Unlike exome sequencing, genome sequencing can identify noncoding variants. Although most confirmed pathogenic variants identified by genome sequencing are within exons [Taylor et al 2015], pathogenic variants have been detected in noncoding regions of *CRB1*, *IFT140*, *PRPF31*, and *USH2A* in individuals with inherited retinal dystrophies [Daich Varela et al 2023].

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

4. Management of Nonsyndromic Retinitis Pigmentosa

Treatment of Manifestations

Cystoid macular edema (CME). Some therapeutic success has been reported with both systemic and topical carbonic anhydrase inhibitors (oral acetazolamide [Diamox] or topical dorzolamide); however, rebound edema can occur with continued use [Fishman & Apushkin 2007].

Cataracts. Approximately 50% of individuals with RP develop cataracts that eventually require lens extraction (with visual improvement in the majority). However, since visual acuity can be reduced because of the incipient cataract or concomitant macular sequela of RP (CME or defects of the retinal pigment epithelium), determining which is the major cause of reduced vision can be difficult. In the presence of macular disease, extraction of lenses when cataracts are in the early stage may not always improve the quality of vision, particularly in younger individuals who still have reasonable accommodation for near tasks.

The timing of lens extraction may change as an individual ages and the visual field becomes more constricted: most individuals with RP with a visual field greater than 10 degrees are not greatly incapacitated by mild to modest posterior subcapsular cataracts, whereas those with a visual field of less than 10 degrees usually report significantly improved vision following lens extraction [Jackson et al 2001].

Individuals with retinitis pigmentosa are at a greater-than-average risk for postoperative inflammation and induced CME. Thus, it is important at the time of lens extraction to avoid unnecessary manipulation of the iris; following surgery it is important to administer anti-inflammatory agents longer than would be indicated for individuals who do not have RP.

Optical aids. Because of the concern of acceleration of retinal degeneration from short-wavelength light exposure, use of UV-A and UV-B blocking sunglasses is recommended. Use of CPF 550 lenses (Corning Photochromic Filter, developed by Corning Medical Optics), 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.

Google Glass® allows minification of the visual field so that a wider field of view can be seen by individuals with loss of peripheral vision. A relatively new wearable device called eSight® provides a live video stream that can be adjusted in terms of magnification, contrast, color, and brightness, to allow optimal vision for the wearer. However, its current cost limits widespread use.

Retinal prostheses. A number of retinal prosthetic devices that can be implanted in an epiretinal, subretinal, or suprachoroidal location to electrically stimulate either the bipolar cells or retinal ganglion cells have been developed (for review, see Hadjinicolaou et al [2015]). These devices have had varying success in facilitating the perception of light, shapes, and movement in individuals with end-stage RP. One such device, the Argus II®, has been FDA approved and is in clinical use in a limited subset of individuals with vision of light perception or worse (no light perception) in the United States and Europe. As such, this is the first FDA-approved treatment for retinitis pigmentosa [da Cruz et al 2016].

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.

Other. Prolonged light deprivation is **not** effective in altering the progression of RP.

Surveillance

Generally Goldmann visual field perimetry (GVF) or full-field static perimetry [Weleber et al 2015] and a full ophthalmoscopic examination with dilation are performed on an annual basis, with more frequent follow up for active complications such as cystoid macular edema.

Modeling of full-field static perimetry with generation of volumetric indices that reflect both the magnitude and extent of visual field sensitivity are used: for monitoring for rate of progression; as endpoints for clinical trials [Bainbridge et al 2015, Weleber et al 2016]; and to explain to individuals the effect of disease progression on visual field [Weleber et al 2015].

Agents/Circumstances to Avoid

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

Increased exposure to light has been demonstrated to accelerate progression in animal models of retinitis pigmentosa, particularly those with pathogenic variants in the gene encoding rhodopsin [Naash et al 1996, LaVail et al 1999]; thus, avoidance of bright light and use of UV-blocking sunglasses are recommended for all individuals with RP.

Smoking has been demonstrated as a strong risk factor for age-related macular degeneration [Seddon et al 1996, Chew et al 2013], and is thought to contribute to retinal damage in retinitis pigmentosa and other inherited retinal degenerations as well; thus, avoidance of smoking is recommended for all individuals with RP.

Pregnancy Management

Women of childbearing age need to be cautioned about potential teratogenic effects of high-dose vitamin A palmitate (see Therapies Under Investigation) to the developing fetus. See Clinical Manifestations for further information about possible progression of disease during pregnancy.

Therapies Under Investigation

Supplementation

Several trials of nutritional supplements to treat retinitis pigmentosa have been conducted with varying success; the results are often controversial [Massof & Fishman 2010]. Some clinicians recommend treatment with antioxidant vitamins similar to what has been proven to slow progression in age-related macular degeneration [Chew et al 2013], while others recommend only those supplements studied specifically in RP.

Vitamin A

- Therapy with 15,000 IU per day of vitamin A palmitate has been reported to possibly slow changes in retinal function as detected by ERG [Berson et al 1993, Massof & Finkelstein 1993]. However, clinical measures such as visual acuity and visual field appear unaffected by vitamin A. Of note, the *only* preparation tested has been vitamin A palmitate.
- High-dose vitamin A should not be used for individuals with ABCA4-deficient Stargardt disease or ABCA4-deficient autosomal recessive RP because it increases the accumulation of the toxic byproduct A2E [Radu et al 2008].
- Vitamin A palmitate therapy is not recommended for those under age 18 years.
- Although liver toxicity with long-term use of vitamin A at 15,000 IU per day 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 palmitate.
- Because long-term high intake of vitamin A daily has been reported to increase several-fold the risk of osteoporosis, bone density should be monitored with such supplementation [Melhus et al 1998, Feskanich et al 2002, Michaëlsson et al 2003].

Docosahexaenoic acid (DHA)

- DHA therapy (1,200 mg/day) showed no effect on disease course in individuals receiving vitamin A palmitate [Berson et al 2004a], although high RBC concentration of DHA correlated with slower decline in visual field sensitivity [Berson et al 2004b].
- DHA 400 mg/day showed no effect on visual acuity or visual field in males with xlRP, although RBC concentration of DHA correlated with preservation of cone ERG function [Hoffman et al 2004].
- A systematic literature review reported some improvement in outcomes with omega-3 fatty acid supplementation, but meta-analysis was not possible and additional studies are required [Hodge et al 2006].
- A later study using a food questionnaire to estimate DHA intake in individuals with RP taking vitamin A palmitate demonstrated a slower decline in visual acuity in those with high DHA intake [Berson et al 2012].

Lutein

- One study 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 [Aleman et al 2001].
- A Phase I/II clinical study showed that lutein supplementation had a significant effect on visual field, but no effect on visual acuity or contrast sensitivity [Bahrami et al 2006].
- A more recent clinical trial of lutein supplementation over four years in individuals also receiving vitamin A palmitate demonstrated no toxic effects from lutein and a slower loss of mid-peripheral visual field than in untreated individuals [Berson et al 2010].

Gene Therapy

Gene therapy is being actively pursued for a number of retinal degenerations; published clinical trials have demonstrated limited success in individuals with *RPE65*-related Leber congenital amaurosis, severe early-childhood-onset retinal dystrophy (SECORD), and disorders with infantile onset or early-childhood onset that are closely related to retinitis pigmentosa [Bainbridge et al 2008, Maguire et al 2008, Jacobson et al 2012, Testa et al 2013, Bainbridge et al 2015, Jacobson et al 2015, Weleber et al 2016].

An ongoing trial is evaluating gene therapy for autosomal recessive *MERTK*-related RP.

Stem Cells

Multiple studies have investigated embryonic stem cells and induced pluripotent stem cells, which can be differentiated in vitro into retinal cell types and transplanted into animal retinas (for review, see Jayakody et al [2015]).

A Phase I/II clinical trial reported no safety concerns of transplanting stem cell-derived retinal pigment epithelial (RPE) cells in a small group of individuals with Stargardt disease, an inherited macular dystrophy, and age-related macular degeneration; however, to date no similar clinical trials have been performed for RP [Schwartz et al 2015].

Other

Triamcinolone injection. A study demonstrated a short-term benefit that was lost after a few months [Scorolli et al 2007].

Intravitreal VEGF inhibitors bevacizumab and ranibizumab. Preliminary data show some success in reducing macular edema and improving visual acuity [Artunay et al 2009, Yuzbasioglu et al 2009].

Hyperbaric oxygen therapy was shown to preserve visual acuity, visual field, and ERG response in people with RP as compared to vitamin A therapy over a ten-year period [Vingolo et al 2008].

Neurotrophic factors have shown promise in treating several animal models of RP. An intraocular implant that secretes ciliary neurotrophic factor (CNTF) demonstrated safety in Phase I trials but showed no therapeutic benefit in Phase II trials [Dandekar et al 2004, Emerich & Thanos 2008, Birch et al 2013].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

5. Genetic Risk Assessment

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Nonsyndromic forms of retinitis pigmentosa (RP) can be inherited in an autosomal dominant, autosomal recessive, or X-linked manner depending on the gene involved. Rare digenic forms also occur (see Causes).

Note: Pedigree analysis may not be reliable in determining mode of inheritance, as both xlRP and arRP pedigrees can be consistent with autosomal dominant inheritance (see Related Genetic Counseling Issues).

Autosomal Dominant RP (adRP) – Risk to Family Members

Parents of a proband. Most individuals diagnosed with adRP have an affected parent; occasionally, a proband with RP may have the disorder as the result of a *de novo* pathogenic variant.

Sibs of a proband

- If a parent is affected, the risk to the sibs is 50%.
- If the RP-related pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is slightly greater than that of the general population (though still <1%) because of the possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with adRP has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected, the parent's family members may be at risk.

Autosomal Recessive RP (arRP) – Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of one RP-related pathogenic variant).
- Heterozygotes for a pathogenic variant causing arRP are asymptomatic in most cases.

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.
- Heterozygotes for a pathogenic variant causing arRP are asymptomatic in most cases.

Offspring of a proband. The offspring of an individual with arRP are obligate heterozygotes for an RP-related pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier (heterozygote) detection. Carrier testing for at-risk relatives requires prior identification of the RP-related pathogenic variants in the family.

X-Linked RP (xlRP) – Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the *OFD1*, *RP2*, or *RPGR* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. Note: If a woman has more than one affected child and no other affected relatives and if the pathogenic variant cannot be detected in her leukocyte DNA, she has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote or the affected male may have a *de novo* pathogenic variant, in which case the mother is not a heterozygote.

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has an pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes and may or may not have symptoms [Andréasson et al 2003, Banin et al 2007].
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is slightly greater than that of the general population (though still <1%) because of the possibility of maternal germline mosaicism.

Offspring of a male proband. Affected males transmit the pathogenic variant to:

- All of their daughters, who will be heterozygotes and may or may not have symptoms;
- None of their sons.

Other family members of a male proband. A male proband's maternal aunts may be at risk of being carriers, and the aunts' offspring, depending on their sex, may be at risk of being carriers or of being affected.

Heterozygote (carrier) detection. Carrier testing for at-risk female relatives is possible if the pathogenic variant in the family has been identified.

Related Genetic Counseling Issues

Determining Mode of Inheritance

Inheritance in families with vertical transmission and affected males and females can be autosomal dominant or X-linked. The possibility of xlRP with clinical expression in heterozygous females should be considered in pedigrees consistent with adRP (male-to-male transmission of RP precludes this possibility) [Churchill et al 2013].

Simplex cases of RP are not necessarily autosomal recessive. Simplex cases (i.e., a single occurrence in a family) represent 10%-40% of all individuals with RP. It is important to stress that simplex cases of RP are not necessarily autosomal recessive and caution should be used in predicting recurrence risk when molecular genetic testing has been uninformative. Possible explanations for a simplex case include the following:

- Autosomal recessive inheritance with no affected sibs
- *De novo* autosomal dominant or X-linked pathogenic variant
- Autosomal dominant or X-linked inheritance with reduced penetrance in prior generations
- Reduced or inaccurate reporting of family history

Prenatal Testing and Preimplantation Genetic Testing

Once the RP-related pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing for RP are possible. However, clinical severity (which can range from mild to severe) and disease phenotype often differ among individuals with the same pathogenic variant; thus, age of onset and/or disease progression cannot be predicted based on the results of molecular genetic testing.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Foundation Fighting Blindness**
  Phone: 800-683-5555
  fightingblindness.org
- **American Council of the Blind (ACB)**
  2200 Wilson Boulevard
  Suite 650
  Arlington VA 22201
  Phone: 800-424-8666 (toll-free); 202-467-5081
  Fax: 202-467-5085
  Email: info@acb.org
  www.acb.org
- **National Federation of the Blind**
  Phone: 410-659-9314
  Email: nfb@nfb.org
  www.nfb.org
- **Retina International**
  Ireland
  retina-international.org

Chapter Notes

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