

Retinitis Pigmentosa

Author: Doctor Christian Hamel¹

Creation Date: July 2003

Scientific Editor: Professor Jean-Jacques de Laey

¹Physiopathologie et thérapie des déficits sensoriels et moteurs, INSERM U 583, 71 Rue de Navacelles, 34090 Montpellier, France. hamel@montp.inserm.fr

[Abstract](#)

[Key-words](#)

[Disease name and synonyms](#)

[Excluded diseases](#)

[Diagnosis criteria / definition](#)

[Differential diagnosis](#)

[Frequency](#)

[Clinical description](#)

[Management including treatment](#)

[Etiology](#)

[Diagnostic methods](#)

[Genetic counselling](#)

[Antenatal diagnosis](#)

[Unresolved questions](#)

[References](#)

Abstract

Retinitis pigmentosa (prevalence 1/4,000) is an inherited retinal dystrophy caused by the loss of photoreceptors and characterized by retinal pigment deposits visible on fundus examination. The most common form of retinitis pigmentosa (RP) is a rod-cone dystrophy, in which the first symptom is night blindness, followed by the progressive loss in the peripheral visual field in day light, and eventually leading to blindness after several decades. In some cases, the clinical presentation is a cone-rod dystrophy (CRD), in which the decrease in visual acuity predominates over the visual field loss. RP is usually non syndromic but there are also many syndromic forms, the most frequent being Usher syndrome (RP + deafness). The tremendous genetic heterogeneity, with 39 currently known genes (31 cloned, 8 mapped) accounting for only 50 % of non syndromic RPs has hampered the molecular diagnosis. In the absence of any efficient treatment, the therapeutic approach is currently restricted to sunlight protection and management of complications (cataract and macular edema). However, therapeutic strategies are emerging from intensive research (gene therapy, neuroprotection, retinal prosthesis).

Key-words

Retinitis pigmentosa, pigment retinopathy, retinal dystrophy, photoreceptor, retinal pigment epithelium.

Disease name and synonyms

Retinitis pigmentosa (RP) belongs to the vast group of pigmentary retinopathies, a generic name that covers all retinal dystrophies featuring the loss of photoreceptors and retinal pigment deposits.

Excluded diseases

[Leber's congenital amaurosis](#) (LCA), which also belongs to the group of pigmentary retinopathies, must be differentiated from RP, although some genes are involved in both retinopathies. RP is clearly different from the macular dystrophies in which the extent of the lesions are limited to the macula. Cone

dystrophies, which are only associated with cones degeneration, must also be excluded, although some genes cause either cone dystrophies or RP. Finally, cone-rod dystrophies that are usually viewed as a subclass of RP will also be described apart as their semiology is different from typical RP (rod cone dystrophy).

Diagnosis criteria / definition

RP is a retinal degenerative disease characterized by pigment deposits in the retina. This is a primary degeneration of photoreceptor rods with secondary degeneration of cones, which explains why patients initially suffer from night blindness.

Functional signs

- Night blindness (nyctalopia) is the earliest symptom
- Photophobia appears later
- Preserved visual acuity in early and mid stages

Visual field

- Patchy losses of peripheral vision
- Ring shape scotoma
- Tunnel vision

Fundus

- Pigmentary deposits resembling bone spicules, at first in peripheral retina
- Attenuation of the retinal vessels
- Waxy pallor of the optic disc
- Various degrees of retinal atrophy

Electroretinogram

- Dramatic diminution in a and b wave's amplitudes
- Predominates on scotopic system (rods) over photopic (cones) system

Differential diagnosis

Various entities resemble retinitis pigmentosa (RP).

Night blindness in non degenerative diseases

- Congenital stationary night blindness. In autosomal forms, symptoms are limited to night blindness, while X-linked forms are associated with a limited visual acuity.
- Fundus albipunctatus, a rare condition in which fine, white deposits are visible in fundus.
- Vitamin A deprivation syndrome

Non evolving pigmentary retinopathies

The aspect of the fundus is often that of salt-and-pepper pigmentary retinopathy or deposits of pigment with various shape, often dot-like.

- Congenital infections like rubella (salt-and-pepper retinopathy) or syphilis (pseudo-retinitis pigmentosa or leopard skin retinopathy).

-Carriers of X-linked disorders like choroideremia, ocular albinism, RP.

-Mitochondrial diseases like Kearns-Sayre syndrome (ophthalmoplegia), although there may be progressive degeneration of photoreceptors.

-Grouped congenital hypertrophy of the retinal pigment epithelium with characteristic bear footprints.

Choroidal dystrophies

In all cases, there is a marked atrophy of the choriocapillaris that is readily diagnosed by the absence of fluorescence in fluorescein angiography.

-Choroideremia, an X-linked disorder accounting for about 2 % of pigmentary retinopathies

-Gyrate atrophy, a very rare autosomal recessive disorder.

Vitreoretinopathies

In these conditions, the vitreous and inner layers of the retina are also affected. Retinal detachment and retinal vasculopathy are often present.

-Retinoschisis, juvenile X-linked retinoschisis (the most frequent), and Goldman Favre syndrome (autosomal recessive with night blindness associated with retinoschisis).

-Hereditary vitreoretinopathies, the most frequent ones being several autosomal dominant conditions known as familial exudative vitreoretinopathy, Wagner disease and Stickler syndrome.

-Inflammatory diseases of the eye, birdshot chorioidoretinopathy, serpiginous retinopathy, multifocal placoid pigment epitheliopathy.

Maculopathies

Large, extended maculopathies may be difficult to differentiate from end stage RP.

-Stargardt disease, due to mutations in *ABCA4*. Null mutations in this gene can also be responsible for authentic RP.

-Sorsby's disease

-Cone dystrophies, in some cases presenting with a minimal rod involvement.

Secondary pigmentary changes

Several diseases may lead to secondary RP with variable disease course.

-Intoxication with various drugs including thioridazine and chloroquine. Although chloroquine usually leads to "bull's eye maculopathy", there are some cases of RP-like pigmentary retinopathies that may continue to progress even after the arrest of drug intake.

-Inflammation (pars planitis, Behcet disease, sarcoidosis, subacute diffuse unilateral

neuroretinitis) may rarely be complicated with RP.

-Sequelae of severe gravidic toxemia, uveal effusion syndrome or trauma.

-Parasitic infections such as onchocercosis.

Frequency

Prevalence of non syndromic retinitis pigmentosa is 1/4,000 (Ammann *et al.*, 1965; Boughman *et al.*, 1980; Jay, 1982).

Clinical description

Non syndromic retinitis pigmentosa

Typical form

RP is a long lasting disease that usually evolves over several decades. However, extreme cases present with a rapid evolution over two decades or a slow progression that never leads to blindness. The disease course can be conveniently divided into three stages.

In the early stage, night blindness is the main symptom. It may be present from the first years of life or may appear during the second decade or even later. Mild night blindness is often ignored by the patients and becomes apparent in the teen ages at evening parties. At this stage, there may be peripheral visual field defects in dim light. However, these defects do not exist or are minimal in day light, so that patients have normal life habits and the disease can appear stable. Diagnosis is difficult to establish at this stage, particularly when there is no familial history (about half the cases). Visual acuity is normal. Fundus examination (**Figure 1**) may seem normal because bone spicule-shaped pigment deposits are not present or rare. Moreover, the attenuation of retinal arterioles is modest and the optic disc is normal. The visual field test reveals scotomas only in scotopic conditions, while the test is usually done in mesopic conditions. Color vision is normal. The electroretinogram (ERG) is the key test; in most cases, it shows a decreased amplitude of the b wave that predominates in scotopic conditions. However ERG may appear normal when only a regional part of the retina is affected, although the maximum ERG should be diminished.

In the mid stage, the clinical picture is complete. Night blindness is obvious with difficulties to drive by night and to walk at evening and in dark staircases. Patients become also aware of loss in the peripheral visual field in day light conditions through stereotypic situations; for example, while driving, they do not see pedestrians or side-coming cars, they miss hands in handshaking and frequently step into various objects. Consequently, patients adapt themselves by avoiding night driving or circulation in unfamiliar places. Dyschromatopsia to pale colors, particularly blue and yellows hues, is often present. In addition, patients

become photophobic, particularly in presence of diffuse light (white cloudy weather). This results into reading difficulties, with a narrow window between insufficient and too bright light. Difficulties with reading are also due to decreased visual acuity, partly because of macular involvement (macular oedema or mild foveomacular atrophy) and subcortical posterior cataract. Fundus examination (**Figure 2**) reveals the presence of bone spicule-shaped pigment deposits in the mid periphery along with atrophy of the retina. Narrowing of retinal vessels is evident and the optic disc is moderately pale. In contrast, the extreme periphery and the macular region appear relatively spared, although mild macular involvement is frequent. The ERG is usually unrecordable in scotopic conditions (rods) and the cone responses (30-Hz flickers, bright light) are markedly hypovolted. Phenotypic features of the disease should be carefully registered to guide towards mutation searches. At this stage, evaluation of the rate of the disease progression, based on several year-to-year examinations (visual acuity, ERG and most importantly visual field testing), is mandatory. Indeed, visual field testing shows mild periphery scotomas that tend to enlarge towards extreme periphery and macular area. Cataract, which usually blurs the optic center, should be removed even when there is macular involvement.

In the end stage, patients can no longer move autonomously, as the result of peripheral vision loss (classical tunnel vision), with few degrees of remaining visual field around the fixation point. Reading is difficult; magnifying glasses are necessary. Photophobia is intense. Fundus examination (**Figure 3**) reveals widespread pigment deposits reaching the macular area. Vessels are thin and the optic disc has a waxy pallor. Fluorescein angiography detects chorioretinal atrophy in the periphery and also in the foveomacular area. The ERG is unrecordable. Even at this stage, the disease progression remains slow, with patients being able to read short passages for years, while totally incapable to move. However, reading becomes impossible when the central visual field vanishes. Usually, patients continue to perceive light, often in the peripheral visual field.

Figure 1: Fundus of RP patient at early stage

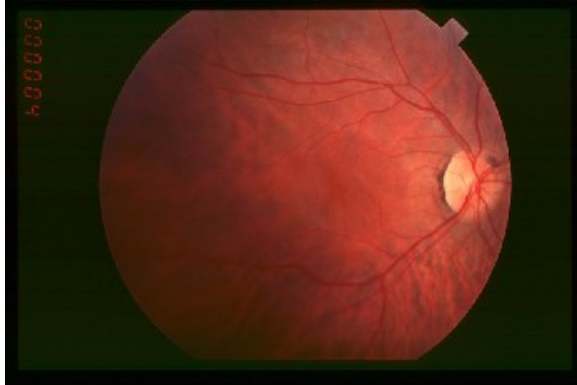
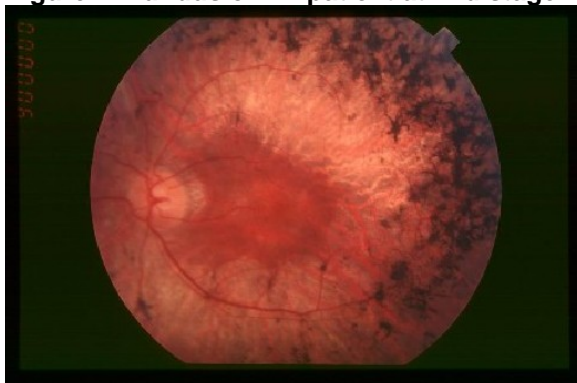
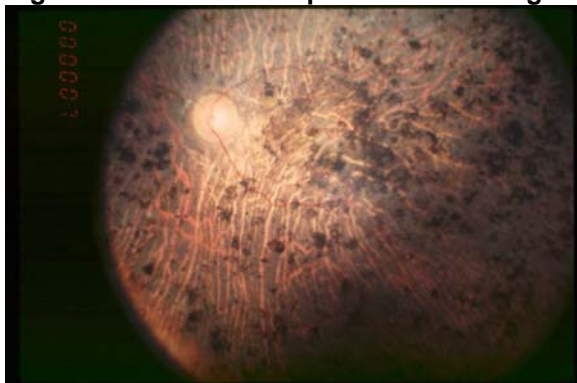


Figure 2: Fundus of RP patient at mid stage



Bone spicule-shaped pigment deposits are present in the mid periphery along with retinal atrophy, while the macula is preserved although with a peripheral ring of depigmentation. Retinal vessels are attenuated.

Figure 3: Fundus of RP patient at end stage



Pigment deposits are present all over the retina. Retinal vessels are very thin and optic disc is pale.

Clinical forms

There are many forms of non syndromic RP that can be classified on the basis of several criteria:

- *Age of onset*

There are cases of congenital or early-onset RP that are often indistinguishable from LCA. In fact *RPE65*, *CRB1*, *CRX*, *TULP1* are genes causing retinal dystrophies that are diagnosed either as LCA or RP, depending on the age of onset.

- *Fundus appearance*

- Absence or scarcity of pigment deposits is frequent in myopia because of retinal pigment atrophy linked to this condition. In other cases, the amount of pigment deposits may vary and do not necessarily reflect the severity of the disease.

- Localization of the lesions. There are regional or sectorial forms in which only one or two quadrants are affected (*RHO*, *PRPF31* mutations). The lesions can also be localized as a ring around the macula (pericentral), the optic disc (parapapillary) or predominantly along retinal veins (paraveinous). In some cases, there is para-arteriolar retinal pigment epithelium preservation (*CRB1* mutations). Finally, there are rare cases of unilateral RP for which a local cause (trauma) should be actively searched for.

- Other lesions. White dots or whitish spots can be present like in retinitis punctata albescens (*RLBP1* mutations). Macular atrophy can be quite prominent from the mid stage of the disease (*RDS* and *CRX* mutations).

- *Mode of inheritance*

- Autosomal dominant forms are usually the mildest forms, with some cases starting after the age of 50 years, although severe disease can also be encountered in these forms. Variations in penetrance are frequent, particularly with *PAP1*, *PRPF31* and *RP1* genes. In genetic counseling, one should always suspect autosomal dominance in apparently sporadic mild cases, especially when ascendants have not been thoroughly examined.

- Autosomal recessive forms start typically during the first decade, although some mild forms can be encountered.

- X-linked forms also start early and are frequently associated with myopia. Although transmission is recessive in most cases, there are some families in which dominant inheritance with affected females is found.

- Digenic form: rare cases have been described in which heterozygous mutations in *ROM1* in combination with heterozygous mutations in *RDS* cause digenic RP. These forms are inherited in a pseudo-dominant pattern (1/4 risk).

Syndromic retinitis pigmentosa

Many syndromes associate with various types of pigmentary retinopathies, including RP. These syndromes will just be listed below as the reader can report to the specific Orphanet entry.

Frequent syndromes

[Usher syndrome](#) is the most frequent syndromic form in which typical RP is associated with neurosensory deafness. About 14 % of RP

cases are Usher syndromes (Boughman *et al.*, 1983). Deafness, generally congenital and stable, may be profound (type 1) or moderate/medium (type 2). In some cases (type 3), deafness occurs during the first decade and worsens progressively. At least 12 genes are responsible for Usher syndrome (for review see Ahmed *et al.*, 2003).

[Bardet Biedl syndrome](#) is less frequent with a prevalence of 1/150.000 (Beales *et al.*, 1999) but the phenotype is characteristic. It associates RP (often of the cone-rod dystrophy type) with obesity, mental retardation, post axial polydactyly, hypogonadism and renal abnormalities that lead to renal failure. At least 7 genes are responsible, with cases of triallelic digenic inheritance.

Less frequent syndromes

- *Renal abnormalities*

-Senior Loken syndrome: severe forms associate a severe RP, sometimes diagnosed as LCA, with nephronophthisis (renal failure frequently requiring transplantation) or manifest a milder RP that is discovered later in life.

-[Alport syndrome](#): deafness, progressive nephritis are associated with yellow flecks around the macula rather than with an authentic RP.

- *Dysmorphic syndromes*

- [Cohen syndrome](#) associates a particular facial dysmorphism (prominent upper incisors) with short stature, mental retardation, long and narrow hands, neutropenia and RP.

-[Jeune syndrome](#) associates a thoracic hypoplasia, brachydactyly, chronic nephritis with RP.

-[Cockayne syndrome](#) associates dwarfism, progeria, mental retardation and retinopathy with fine granular spots.

- *Metabolic diseases:*

-[Methylmalonic aciduria with homocystinuria](#) is caused by genetic defects in enzymes that metabolize vitamin B12. Rare cases present with macular atrophy, salt-and-pepper retinopathy and vascular attenuation.

-[Abetalipoproteinemia](#) (Bassen Korntzweig disease) with progressive ataxia, steatorrhea, reduction of plasma lipids and pigmentary retinopathy resembling retinitis punctata albescens in some cases.

-Bietti's disease with microcrystalline deposits in fundus and cornea and atrophic RP.

-[Cystinosis](#): typical crystals are found in the cornea along with a pigmentary retinopathy in a highly photophobic, short patient. Accumulation of cystine in other body parts leads to

hypothyroidism, diabetes mellitus and renal failure.

-Mucopolysaccharidoses, characterized by facial and bony changes, mental retardation and corneal clouding. Only [types I, II](#) and [III](#) show pigmentary retinopathy.

-Peroxisomal disorders: except for the rhizomelic chondrodysplasia punctata, all children with disorders of peroxisomal assembly who survive long enough develop pigmentary retinopathy.

-Zellweger (cerebro-hepato-renal) syndrome.

-Neonatal adrenoleukodystrophy with leopard spots in fundus.

-Infantile refsum disease with elevated phytanic acid and pigmentary retinopathy with characteristic prominent macular involvement.

-[Adult refsum disease](#) with highly elevated phytanic acid, anosmia, deafness and RP.

-[Hyperoxaluria type I](#) with retinal atrophy in spots.

- *Neurological diseases*

-Neuronal ceroid lipofuscinosis also known as amaurotic idiocies, associates mental retardation, seizures, ataxia and retinal degeneration. The retinal disease starts with macular involvement (red-cherry spot) and later spreads to peripheral retina.

-[Autosomal dominant cerebellar ataxia type II \(SCA7\)](#) shows a retinal disease which often begins with a granular macula and then spreads out to the whole retina.

-Myotonic dystrophy shows cataract and sometimes pigmentary retinopathy.

-Hallervorden-Spatz syndrome shows progressive dysarthria and dementia, iron deposition and flecked type retinopathy with bull's eye maculopathy.

-[Joubert syndrome](#): vermian hypoplasia, renal cysts and pigmentary retinopathy.

Management including treatment

Currently, there is no therapy that stops the evolution of pigmentary retinopathies or restore vision. However, several therapeutic strategies aim at slowing down the degenerating process, as well as treating complications and helping patients to cope with the social and psychological impact of blindness.

Slowing down the degenerating process

Light protection

Clinical evidence and data from animal studies indicate that some genetic types of pigmentary retinopathies are partly light-dependent (Wang *et al.*, 1997). Thus, patients with pigmentary retinopathies are recommended to wear dark glasses outdoors. Wearing of yellow-orange spectacles minimizes photophobia. Eyeshade

and lateral protection help to protect against dazzling side coming light rays.

Vitaminotherapy

Vitamins A and E may protect the photoreceptors by trophic and anti-oxidant effects, respectively. Previous studies have demonstrated that long term (5-12 years) vitamin A supplementation at doses of 15,000 units per day slightly slows down the loss in ERG amplitude, while vitamin E at 400 units per day has adverse effects (Berson *et al.*, 1993). However, the conclusions of this study were debated (Massof *et al.*, 1993) and there is no current consensus as to the usefulness of vitamin A treatment. If vitamin A supplementation is proposed, levels of serum retinol (normal <3.49 $\mu\text{mol/l}$, i.e. <1 mg/l) and triglyceridemia (normal <2.13 mmol/l, i.e. <0.19 g/l) should be regularly checked, as well as liver enzymes (AST, ALT and alkaline phosphatase) since vitamin A storage occurs mainly in this organ.

Treatments of complications

The most frequent complications are cataract and macular edema.

Cataract

It is a posterior central subcapsular cataract with a clear nucleus, which is usually present at mid stage in the evolution of the disease. Although cataract is not widespread, its central position blurs the remaining central visual field, is sight restricting and generates photophobia. Phacoemulsification with implantation of an intra ocular lens is therefore required.

Macular edema

Macular edema occurs frequently, causing a decrease in the visual acuity. Chronic macular edema of RP patients usually responds well to treatments with inhibitors of the carbonic anhydrase, such as acetazolamide sodium at a daily dose of 500 mg or less (Cox *et al.*, 1988). In some cases, acute episodes of macular edema also respond well to inhibitors of the carbonic anhydrase. Topical administration of dorzolamide is inefficient (Grover *et al.*, 1997).

Inflammatory reactions

Mild inflammatory reactions occur frequently in the vitreous, and are often associated with a macular edema, a vascular diffusion visible on fluorescein angiogram and an early cataract. Although these reactions do not require a specific treatment, some cases present with large exudates in the peripheral retina (pseudo Coats), which lead to retinal detachment and rapid evolution towards blindness. This latter

complication has recently been found recurrently in RP linked to *CRB1* mutations (den Hollander *et al.*, 2001). Cryotherapy or laser treatment are required to resorb the exudates.

Others

Myopia is associated with X-linked RP, requiring management and routine examinations as for non RP patients. Glaucoma is not associated with RP but the presence of increased intraocular pressure in RP patients should be cautiously checked in order to prevent more rapid deterioration of the visual field.

Management of blind patients

Psychological help is often necessary when reaching milestones in the disease course, such as announcement of the disease, occurrence of moving difficulties and loss of reading. This support can be provided by both professionals and associations of patients. Patients should be oriented towards institutions that help them to rehabilitate (short- and medium-stay stages), such as ARAMAV (Nîmes, France) and CRAM (Marly-le-Roi, France), and provide them with new professional abilities.

Future treatments

Tremendous efforts are being invested to identify the involved genes, to unravel the underlying pathophysiologic mechanisms and to find efficient therapeutic strategies. Therapeutic researches are focused around three main topics. Nevertheless, one should be aware that none of these future treatments are currently used.

Treating the cause of the disease

- *Gene therapy*

This approach requires that genes be identified and that efficient genotyping methods be available. The currently known genes responsible for RP account for at most 50 % of the cases, and strategies to test in a short time several tenths of genes for a single patient DNA are only emerging. Also, while the strategy is relatively simple for RP due to loss-of-function (usually recessively inherited), it is more complicated for RP due to dominant negative pathogenic mechanisms (ribozymes, gene therapy). Although the short-term efficacy of gene therapy has been recently demonstrated in animal, its long-term efficiency has not been established and the most appropriate vectors and promoters have not yet been clearly identified. Most importantly, the potential hazards of gene therapy (cell proliferation, autoimmunity or degeneration due to inappropriate transgene expression level or localization) in non-life threatening diseases

seem overwhelming in regards to its potential benefits.

- *Pharmacological treatment*

It offers the advantages of using known drugs which can be stopped at any time, but the cause and the pathophysiology of the disease must be known. Pharmacological agents can compensate for a biochemical defect, enhance or inhibit the activity of various effectors.

- *Neuroprotection*

This is a vast topic that is aimed at finding agents that protect rods and cones against apoptosis. Several neurotrophic factors, including ciliary neurotrophic factor, glial-derived neurotrophic factor, cardiotrophin-1, have some efficacy in animal models but their effects and long term efficacy must be further investigated. Cone death in typical RP is thought to be caused by rod loss. This hypothesis suggests that grafts of rods from healthy retinas or use of rod-derived factors protecting cones may be beneficial (Mohand-Said *et al.*, 1998).

Restoring visual function

In advanced stages of the disease, the goal is to restore some visual function in patients.

- *Cell or organ therapy*

Various strategies using retinal cells from fetuses, adult retina, retinal pigment epithelium (RPE) cells or layers of photoreceptors have been tried but their efficiency in human pigimentary retinopathies has not yet been proven. However, graft of RPE in diseases caused by a genetic defect in this tissue seems to have a reasonable chance of success.

- *Retinal prosthesis*

Microphotodiodes arrays that replace degenerated photoreceptors, or more sophisticated devices that capture light and stimulate the retina, the optic nerve or the visual cortex have been developed. Improvements in the resolution of some of these systems are to be expected.

Etiology

RP are genetic disorders inherited as mendelian traits in most cases, with some rare RP cases due to mitochondrial DNA mutations (Mansergh *et al.*, 1999). Cases of digenic diallelic (RDS/ROM1) or triallelic (BBS2/BBS6) inheritance, uniparental isodisomy and incomplete penetrance have been also described (Rivolta *et al.*, 2002).

In 1990, the first gene shown to be involved in RP was that of *rhodopsin*, which encodes the rod visual pigment (Dryja *et al.*, 1990). Since then, it has been established that many genes

cause RP

(<http://www.sph.uth.tmc.edu/retnet/sum-dis.htm>). To date, 39 known genes have been identified in non syndromic RP, including 13 for autosomal dominant- (12 cloned, 1 mapped), 21 for autosomal recessive- (17 cloned, 4 mapped) and 5 for X-linked- (2 cloned, 3 mapped) inheritance. It has been estimated that the cloned genes account for about 50 % of dominant RP, 30 % of recessive RP and approximately 80 % of X-linked RP, indicating that many genes remain to be identified.

These genes products localize in rod (sometimes rod and cones) photoreceptors, and are involved in various metabolisms, and in their supporting tissue, *i.e.* the retinal pigment epithelium. In RP, they include proteins of rod visual transduction (rhodopsin, alpha and beta subunits of the rod phosphodiesterase, alpha and beta subunits of the rod cGMP gated channel and arrestin), cytoskeleton proteins (peripherin/RDS, ROM1, fascin, prominin like 1), proteins presumably involved in trafficking (RPGR, RP1, RP2), in photoreceptor differentiation (NRL, PNR transcription factor), in mRNA splicing (PRPC8, HPRP3, PRPF31), in nucleotide metabolism (pim1 kinase, IMPDH1) or in other metabolisms (tubby, tubby like protein 1, CRB1, MITS2). In addition, RP is also caused by mutations of genes encoding proteins which are involved in the retinol metabolism and are either expressed in photoreceptors (ABCA4 which also causes Stargardt's disease) or in the RPE (RPE65, the light dependent isomerase RGR, the 11-cis retinoid transporter CRALBP, the lecithin retinol acyl transferase LRAT).

The genetic heterogeneity of RP is difficult to correlate with the fairly homogeneous phenotype of the disease. Photoreceptors, and particularly rods, may require a highly regulated environment to function properly and any alteration of this environment may activate apoptotic pathways, causing loss of rods and cones. Rods have a very elongated outer segment that contains several hundreds of membrane discs, in which visual transduction occurs. Discs contain huge amounts of visual transduction proteins, particularly rhodopsin (~ 4 X 10⁷ molecules per rod) and cytoskeleton proteins. Discs are phagocytosed daily by the RPE at the apex of the rod outer segment, and this mechanism is compensated by a daily boost of disc renewal at the base of the outer segment. This requires an intense activity of mRNA and protein synthesis, as well as an important protein trafficking from the rod inner segment through the connecting cilium to the rod outer segment. This cellular activity generates an important energy consumption, requiring high content in mitochondria and oxygen, and mechanisms to

protect against the side effects of mitochondrial metabolism.

Loss of the rod outer segment may be caused by mutations that lead to its destabilisation (mutations in cytoskeleton or trafficking proteins). This would considerably shorten the photoreceptor layer and expose the photoreceptor cell body to high pressure levels in oxygen, hence oxygen toxicity. In addition, diminution in the ability to respond to the high demand in energy or mRNA/protein synthesis may somewhat destabilize the outer segment. Other mechanisms that may be involved are calcium toxicity or metabolic exhaustion by constant opening of the cGMP-gated channel, due to defective visual transduction proteins.

Finally, alterations in critical RPE functions, such as disc phagocytosis or retinol metabolism, may also deregulate the fine balance of photoreceptor metabolisms.

Identification of the causative genes is the first necessary step towards the understanding of RP pathophysiology. With the assistance of genetic databases, it can be reasonably assumed that most genes responsible for autosomal dominant and X-linked RP will be known within the next few years. This will not be as straightforward in autosomal recessive RP and some sporadic cases, as these forms seem to be associated with an extreme genetic diversity. The second step is to identify the common pathogenic pathways in which the identified genes are involved. This implies the development of animal models and long lasting experiments based on cell and molecular biology techniques. The third step is to conduct therapeutic trials (gene therapy, cell therapy). In some cases, the identification of responsible genes has already suggested a relatively simple pharmacological approach such as 9-cis retinal supply in RPE65^{-/-} mice (Van Hooser *et al.*, 2000) or NAD analogues supply in future IMPDH1 defective individuals (Bowne *et al.*, 2002).

Diagnostic methods

Clinical diagnosis is based on the presence of night blindness and peripheral visual field defects, lesions in fundus, hypovolted ERG traces and worsening of these signs. Full field ERG is the key test, particularly when patients are asymptomatic and show normal fundus at early stages of the disease, or in autosomal dominant forms with variable penetrance, since it is usually hypovolted before the appearance of clinical signs (night blindness). It is important to ascertain the diagnosis by repeating the examination one or two years after it has been first established. Multifocal ERG and electro oculogram are not essential to establish the diagnosis.

Systematic molecular diagnosis is not currently performed due to the tremendous genetic heterogeneity of the disease and to the unavailability of rapid and large-scale mutation screening techniques. However, several laboratories are developing strategies for the rapid identification of mutations in the most frequently involved genes. These genes are :

- *RPGR* that accounts for at least 10 % of all cases of non syndromic RP, including 55 % of X-linked RP and 25 % of sporadic RP. It is also involved in cases of X-linked cone or macular dystrophies.

- *RHO* that accounts for 15 to 20 % of dominant non syndromic RP cases.

- *USH2A* may account for 1/3 to 1/2 of Usher cases and may be involved in 14 % of recessive non syndromic RP.

Molecular diagnosis can be performed by research laboratories with other genes in families who have participated in genetic research and in which the responsible gene has been identified.

Genetic counselling

Once the diagnosis is made, patients should be informed and familial surveys are recommended. Genetic counseling is always advised since all genetic forms can be encountered in RP. A precise phenotypic diagnosis is always mandatory and is particularly useful in the absence of familial history or in sporadic cases.

Antenatal diagnosis

Antenatal diagnosis (amniocentesis) raises an ethical issue: it can be performed in families in which the responsible gene has been identified, particularly in families with early onset and severe RP. Whether the investigative risks associated with amniocentesis are justified in a non life-threatening disease is however questionable.

Unresolved questions

Cloned genes account for 40 to 54 % of the autosomal dominant cases, 61 to 89 % of the X-linked cases, and probably less than 1/3 of the autosomal recessive cases, not taking into account all the sporadic cases (45 % of all RP cases). Therefore, it can be broadly estimated that at least half of the genes have yet to be discovered. It is anticipated that modifier genes play important roles, in particular in incomplete penetrance of autosomal dominant RP and in sporadic cases. Those modifier genes, that could also be used for therapeutic prospects, remain to be discovered. Among the products of the cloned genes, they are many whose function is not as yet known or poorly defined. This is the case for *RP1*, *PAP1*, *IMPDH1*, *CRB1*, *RPE65*,

TULP1, *MERTK*, *PROML1*, *TUB*, *RP2* and *RPGR*.

The precise steps that lead from a gene mutation to photoreceptor degeneration remain to be elucidated. In addition, it is likely that several apoptotic pathways are involved in photoreceptor loss, sometimes concurrently, and this also needs to be carefully studied. This knowledge is critical to design therapies.

The efficacy of various potential treatments has to be proven in large animal models and in humans. For example, gene replacement therapy for RDS in mouse improves photoreceptor ultrastructure, but there is no significant effect on photoreceptor cell loss (Sarra *et al.*, 2001).

References

Ahmed ZM, Riazuddin S, Riazuddin S, Wilcox ER (2003). The molecular genetics of Usher syndrome. *Clin. Genet.* 63, 431-444.

Ammann F, Klein D, Franceschetti A (1965). Genetic and epidemiological investigation of pigmentary degeneration of the retina and allied disorders in Switzerland. *J. Neurol. Sci.* 2, 183-196.

Beales PL, Elcioglu N, Woolf AS, Parker D, Flinter FA (1999). New criteria for improved diagnosis of Bardet-Biedl syndrome : results of a population survey. *J Med Genet* 36, 437-446.

Berson EL, Rosner B, Sandberg MA, Hayes KC, Nicholson BW, Weigel-DiFranco C, Willett (1993). A randomized trial of vitamin A and vitamin E supplementation for retinitis pigmentosa. *Arch Ophthalmol* 111, 761-772.

Boughman JA, Conneally PM, Nance WE (1980). Population genetic studies of retinitis pigmentosa. *Am. J. Hum. Genet.* 32, 223-235.

Boughman JA, Vernon M, Shaver KA (1983). Usher syndrome : definition and estimate of prevalence from two high-risk populations. *J. Chronic Dis.* 36, 595-603.

Bowne SJ, Sullivan LS, Blanton SH, Cepko CL, Blackshaw S, Birch DG, Hughbanks-Wheaton D, Heckenlively JR, Daiger SP (2002). Mutations in the inosine monophosphate dehydrogenase 1 gene (*IMPDH1*) cause the RP10 form of autosomal dominant retinitis pigmentosa. *Hum Molec Genet* 11, 559-568.

Cox SN, Hay E, Bird AC (1988). Treatment of chronic macular edema with acetazolamide. *Arch Ophthalmol* 106, 1190-1195.

den Hollander AI, Heckenlively JR, van den Born LI, de Kok YJM, van der Velde-Visser SD, Kellner U, Jurklics B, van Schooneveld MJ, Blankenagel A, Rohrschneider K, Wissinger B, Cruysberg JRM, Deutman AF, Brunner HG, Apfelstedt-Sylla E, Hoyng CB, Cremers FPM (2001). Leber congenital amaurosis and retinitis pigmentosa with coats-like exudative vasculopathy are associated with mutations in

the crumbs homologue 1 (*CRB1*) gene. *Am J Hum Genet* 69, 198-203.

Dryja T.P., McGee T.L., Reichel E., Hahn L.B., Cowley G.S., Yandell D.W., Sandberg M.A., Berson E.L (1990). A point mutation of the rhodopsin gene in one form of retinitis pigmentosa. *Nature* 343, 364-366.

Grover S, Fishman GA, Fiscella RG, Adelman AE (1997). Efficacy of dorzolamide hydrochloride in the management of chronic cystoid macular edema in patients with retinitis pigmentosa. *Retina* 17, 222-231.

Hamel CP, Griffioen J-M, Bazalgette C, Lasquelles L, Duval P-A, Bareil C, Beaufrère L, Bonnet M, Eliaou C, Marlhens F, Schmitt-Bernard CF, Tuffery S, Claustres M, Arnaud B (2000). Génétique moléculaire des rétinopathies pigmentaires : identification de mutations de gènes *CHM*, *RDS*, *RHO*, *RPE65*, *USH2A* et *XLR51*. *J F Ophtalmol* 23, 985-995.

Jay M (1982). On the heredity of retinitis pigmentosa. *Br. J. Ophthalmol.* 66, 405-416.

Mansergh FC, Millington-Ward S, Kennan A, Kiang A-S, Humphries M, Farrar GJ, Humphries P, Kenna PF (1999). Retinitis pigmentosa and progressive sensorineural hearing loss caused by a C12258A mutation in the mitochondrial *MITS2* gene. *Am J Hum Genet* 64, 971-985.

Massof et al. (1993). Responses to the Berson study. *Arch Ophthalmol* 111, 1456-1466.

Mohand-Said S, Deudon-Combe A, Hicks D, Simonutti M, Forster V, Fintz AC, Leveillard T, Dreyfus H, Sahel JA (1998). Normal retina releases a diffusible factor stimulating cone survival in the retinal degeneration mouse. *Proc Natl Acad Sci USA* 95, 8357-8362.

Rivolta C, Sharon D, DeAngelis MM, Dryja TP (2002). Retinitis pigmentosa and allied diseases: numerous diseases, genes, and inheritance patterns. *Hum Molec Genet* 11, 1219-1227.

Sarra G-M, Stephens C, de Alwis M, Bainbridge JWB, Smith AJ, Thrasher AJ, Ali RR (2001). Gene replacement therapy in the retinal degeneration slow (*rds*) mouse: the effect on retinal degeneration following partial transduction of the retina. *Hum Molec Genet* 10, 2353-2361.

Van Hooser JP, Aleman TS, He Y-G, Cideciyan AV, Kuksa V, Pittler SJ, Stone EM, Jacobson SG, Palczewski K (2000). Rapid restoration of visual pigment and function with oral retinoid in a mouse model of childhood blindness. *Proc Natl Acad Sci USA* 97, 8623-8628.

Wang M, Lam TT, Tso MOM, Naash MI (1997). Expression of a mutant opsin gene increases the susceptibility of the retina to light damage. *Vis Neurosci* 14, 55-62.