



A brief review of retinitis pigmentosa and the identified retinitis pigmentosa genes

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The family of inherited ocular diseases that is collectively known as retinitis pigmentosa is a major cause of progressive retinal disease worldwide. As such, this family of diseases has been the object of much scientific scrutiny, both clinical and basic. The recent application of molecular genetic analyses has heralded the rapid elucidation of the underlying gene defects in many cases. In this article, the fundamental clinical and electroretinographic characteristics of retinitis pigmentosa will be recalled. Additionally, the current understanding of the genetic causes of retinitis pigmentosa will be reviewed, and the identified causative genes will be classified into groups related by function.

INTRODUCTION

Retinitis pigmentosa (RP) has been the name for over 140 years for a number of related dysfunctions of the retina with a combined incidence of approximately 1/3500 [1,2]. There are many forms of these diseases now described, and a variety of partial and complete synonyms for the term “retinitis pigmentosa” have been used in the literature [3]. The similarities that have led to the common grouping of these diseases are based on clinical symptoms, electroretinographic phenotype, and/or genetics. Simultaneously, several classification schemes have been proffered to distinguish the diseases based primarily on the variability of these three diagnostic indices. The current proliferation of genetic knowledge (summarized at RetNet), however, is generating rapid evolution of the systematic approaches to classification of RP diseases. In this article, the spectrum of RP diseases will briefly be reviewed in terms of the clinical, electroretinographic, and genetic characteristics, and the characterized causative genes will be divided according to function. Potential mechanisms of photoreceptor cell degeneration have been recently reviewed [3-5], and will not be treated in depth.

In addition to the typical forms of RP, there are a number of related, or allied, diseases. These may be similar by any of the three diagnostic criteria mentioned above. There are also syndromic forms of RP, in which the disease is present as a component of a multisystem disorder. Where relevant, relationships between RP and these allied diseases and syndromes will be noted. Recent reviews have summarized current research on a number of these diseases, including Leber congenital amaurosis [6], Stargardt disease and fundus flavimaculatus [7], macular degeneration [8], cone dystrophy [9], and the Refsum diseases [10]

CLINICAL DESCRIPTION

Historically, RP patients were believed to suffer from retinal inflammation in conjunction with observed retinal pigmentary changes [1]. Inflammation is no longer considered causal in RP, and cases of true RP are now viewed as genetic in origin. The pigmentary changes remain a common factor in RP diagnoses. Typically, these result from the release of pigment by degenerating cells in the retinal pigment epithelium (RPE). The pigment granules accumulate in perivascular clusters, known as “bone-spicule formations” due to their morphological appearance, in the neural retina. Consequently, early in the disease the pigmented posterior pole of the eye, the fundus, develops a mottled or granular appearance. This is followed by the development of bone-spicule pigmentary deposits overlying the depigmented fundus. Variability in the course of pigmentary changes can cause hypopigmentation, translucence, or window-like holes through the RPE, and rounded clumps of pigment to form in the neural retina [11].

In typical cases, known as rod-cone RP, the rods are the predominantly affected photoreceptor cells [1,11]. This generates a number of characteristic, clinical symptoms including night blindness at an early age or stage of the disease, and bilateral symmetric loss of the mid-peripheral visual fields. Although there is usually relative preservation of macular vision, the visual field defects gradually increase both centrally and peripherally. With progression, cone photoreceptor cells are also affected and day vision and central visual acuity are compromised. The rate of visual failure is variable, but total blindness is eventually possible. The final common pathway of photoreceptor cell death is apoptosis [4,12-14].

A common variant of RP shows the simultaneous involvement of cone photoreceptor cells [1,9,15,16]. These forms, referred to as cone-rod dystrophy or cone-rod degeneration, show a more central loss of the visual field and greater early changes to the cone dominated central retina. The visual symptoms, however, are pan-retinal and often include loss of night vision and peripheral visual fields. The allied diseases of cone

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dystrophy and macular degeneration are disorders of the central retina in which the cones are the predominantly affected photoreceptor cells. In these cases the central visual fields are lost, while night and peripheral vision are preserved.

The age of onset of RP can vary from infancy through late middle age [1,17]. The age at which symptoms become clinically apparent is correlated with the mechanism of inheritance (see below): X-linked RP, autosomal recessive RP, and autosomal dominant RP generally have their onsets at successively greater ages, although the age ranges overlap considerably. Frequently, a case may present with visual symptoms in late adolescence. Leber congenital amaurosis, an RP allied disease, is a severe congenital retinal dystrophy. Syndromic forms usually present at younger ages than typical cases.

As the retina atrophies, the retinal blood vessels attenuate [1,15]. This, in turn, causes ophthalmoscopically visible changes in the color of the optic nerve head through which the vessels enter the eye.

In summary, a typical case of RP will show atrophy and pigmentary changes to the retina and RPE, early night blindness, loss of the visual fields, loss of central visual acuity, attenuation of the retinal vasculature, and changes to the optic nerve head during the course of the disease. In atypical cases of RP or in the closely related allied diseases, any combination of these symptoms may be altered to a greater or lesser extent. This heterogeneity has, in part, led to the difficulties in consistent clinical classification of the various forms of RP.

ELECTRORETINOGRAPHY

A tool now central to the diagnosis and classification of RP is the electroretinogram (ERG) [15,18-20]. In this procedure, photoreceptor cells are either dark adapted (scotopic ERG) or adapted to a specific level of light (photopic ERG), and then stimulated with a brief flash of light. The summed electrical response of the retina is recorded extraocularly with a contact lens electrode. The scotopic ERG selectively measures the response of the rod photoreceptor cells, while the photopic ERG measures that of the cones. An ERG under dark adapted conditions with stimulation by a sufficiently bright white light flash, the mesopic ERG, measures a response from both types of photoreceptor cells. The initial recorded response of the mesopic ERG is a negative potential reflecting the closure of cyclic nucleotide gated cation channels in the photoreceptor outer segment membrane (see below). Subsequently, the ERG shows a positive displacement reflecting the post-photoreceptor cell neuronal activity [15,20,21]. In typical RP, the rod-cone disease manifests initially as alterations of the scotopic ERG and shows a proportional loss of the photoreceptor cell and post-photoreceptor components of the ERG. With cone-rod dystrophy, photopic ERG changes precede those of the scotopic ERG, but the rod response is eventually affected. In cone dystrophy, the photopic ERG is disrupted while the scotopic ERG remains stable. Retinal degenerations that limit damage to the macula generally damage too few cells to cause a measurable distortion of the ERG. In some cases of RP, the post-photoreceptor cell components of the ERG b-wave are disproportionately disrupted, a circumstance known as a nega-

tive, or electronegative, ERG. By the end stages of RP, the ERG responses are extinguished [20,22].

GENETIC CLASSIFICATION

Early genetic classifications of RP were derived mainly from the modes of inheritance: autosomal dominant, autosomal recessive, X-linked, or mitochondrial. Cases for which no family history was evident were known as isolate, sporadic, or simplex. With the advents of linkage mapping based on the direct analysis of DNA, of positional cloning, and of the molecular analysis of candidate genes, the description of genetic loci for RP has exploded. There are now 36 known or predicted RP genes (summarized at RetNet), and many more loci for allied diseases and syndromic forms. It has been pointed out that there are over 70 loci that cause photoreceptor dysfunction or degeneration in *Drosophila*, and a similar number may be expected in humans [23]. In general, RP genes are known or expected to be expressed in the photoreceptor cells of the retina or in the RPE. In the cases of 19 of the RP loci, the precise gene has been described. These known genes can be grouped into several functional classes.

The Visual Cascade: The most common group of genes mutated in RP are those encoding proteins of the visual cascade of the photoreceptor cell outer segment. The visual cascade is the process by which the energy of a photon of visible light is converted into a neuronal signal that is eventually perceived as sight [24]. The cascade begins with the adsorption of light by rhodopsin. Activated rhodopsin stimulates a heterotrimeric G-protein, transducin, that in turn releases the photoreceptor cell specific phosphodiesterase (PDE6) from its inhibitory subunits. The resulting hydrolysis of cGMP allows a cyclic nucleotide gated cation channel in the plasma membrane to close, hyperpolarizing the cells, and transmitting the neuronal signal. The cascade is terminated at several levels, including the phosphorylation of rhodopsin by rhodopsin kinase, the subsequent binding of phosphorylated rhodopsin by arrestin, and by the hydrolysis of bound GTP by the intrinsic GTPase activity of the transducin α subunit.

The genes for the opsin protein of rhodopsin (*RHO*) [25,26], the catalytic α (*PDE6A*) [27] and β (*PDE6B*) [28-30] subunits of PDE6, the α subunit of the rod cyclic nucleotide gated channel (*CNGA1*) [31], and arrestin (*SAG*) [32-34] are known to be mutated in cases of RP. Rhodopsin mutations are the most common cause of RP, and account for as many as 1/3 of the 16% of RP cases that are autosomal dominant, as well as rare cases of autosomal recessive RP [1,35]. In addition, several of these genes are mutated in RP-related allied diseases. These include mutations to rhodopsin [36], α transducin (*GNAT1*) [37], β PDE6 [38], rhodopsin kinase (*RHOK*) [39], and arrestin [40] in congenital stationary night blindness; to guanylate cyclase activator 1A (*GUCA1A*) in cone dystrophy type 3 [41]; to the retina-specific guanylate cyclase (*GUCY2D*) in cone-rod dystrophy type 6 [42,43] and Leber congenital amaurosis type 1 [44]; and to the α subunit of the cone cyclic nucleotide gated cation channel (*CNGA3*) in rod monochromacy [45]. The three cone opsin genes (blue, *BGP*; green, *GCP*; and red, *RCP*) are mutated in a variety of well

described color vision variations and defects [46,47], including occasional progressive cases of macular atrophy [48]. Consistent with the photoreceptor cell specific function of the visual cascade, none of the relevant genes are mutated in syndromic forms of RP.

The Visual Cycle: The second common group of genes mutated in RP are those encoding proteins of the visual cycle. The visual cycle is the series of biochemical steps that provide and recycle the chromophore of rhodopsin, 11-*cis*-retinaldehyde [49-51]. Vitamin A, all-*trans*-retinol, is delivered to the RPE from the systemic circulation bound to serum retinol binding-protein. Within the RPE cells, the all-*trans*-retinol is bound to cellular retinol binding-protein and delivered to lecithin retinol acyltransferase for esterification. Subsequent hydrolysis of the ester bond by an isomerohydrolase provides the energy to isomerize the all-*trans*-retinol to 11-*cis*-retinol [52], in a process thought to involve a protein known as RPE65 [53]. The resulting 11-*cis*-retinol binds cellular retinaldehyde binding-protein (CRA1BP), which delivers it to 11-*cis* retinol dehydrogenase 5 for conversion to 11-*cis*-retinaldehyde. This molecule is transported extracellularly, possibly on interphotoreceptor retinoid binding-protein [54], taken up by the photoreceptors, and bound to the opsin protein by a protonated Schiff-base linkage [55]. Photoisomerization to all-*trans*-retinaldehyde initiates the visual cascade discussed above. The all-*trans*-retinaldehyde, meanwhile, is released from the opsin to the photoreceptor outer segment disc membrane. In rod cells, the released chromophore binds, via a Schiff base linkage, to phosphatidylethanolamine to form N-retinylidene-phosphatidylethanolamine. This substrate is then pumped into the cytoplasm by the ATP-binding cassette transporter of rods (ABCR) [56,57], converted to the alcohol form by a retinol dehydrogenase, and released for transport to the RPE and re-entry into the cycle.

Thus far, the genes encoding RPE65 (*RPE65*) [58], CRA1BP (*RLBP1*) [59], and ABCR (*ABCA4*) [60,61] are known to be mutated in RP. In addition, *RPE65* has been found to be mutated in some cases of Leber congenital amaurosis [62,63], serum retinol binding-protein (*RBP4*) is mutated in rare cases of RPE degeneration [64], and the 11-*cis* retinol dehydrogenase 5 of the RPE (*RDH5*) is mutated in a form of congenital stationary night blindness known as fundus albipunctatus [65,66]. *ABCA4* was first identified as the gene mutated in Stargardt macular dystrophy and fundus flavimaculatus [67], and it has a complex set of mutation phenotypes in addition to classic RP, including both cone-rod and macular dystrophies (for recent reviews see: [7,8,68,69]). Heterozygous *ABCA4* mutations have also been implicated in age-related macular degeneration [70,71], although whether these mutations are causal for the disease remains controversial [8]. There are no known syndromic forms of RP due to mutations in visual cascade genes.

The recent description of RP associated mutations in the RPE-retinal G-protein coupled receptor (*RGR*) [72] opens up new dimensions to the visual cycle and its connection to RP. This seven transmembrane domain receptor, a close relative of rhodopsin, is found in the support cells for the photorecep-

tors, the RPE and the Muller glia. In antithesis to rhodopsin, the RGR protein is coupled to all-*trans*-retinal that is isomerized to 11-*cis*-retinal upon light exposure [73]. Although the role of the RGR in retinal cell biology is not yet clear, it is likely that the proteins in the RPE and Muller glia that deliver vitamin A derivatives specifically to and from this molecule will also be candidates for RP mutations.

Tetraspanins: Two of the known RP genes appear to encode structural proteins of the photoreceptor. These are the genes for peripherin/RDS (*RDS*) and ROM1 (*ROM1*), proteins that together form heterotetramers at the margins of the rod outer segment discs [8]. Both of these genes encode 4-transmembrane domain proteins that are divergent members of the tetraspanin superfamily [74]. Mutations in *RDS* can be directly causal for RP [75,76], but so far the mutations in *ROM1* that are definitively pathogenic have occurred only in patients heterozygous for mutations at both *RDS* and *ROM1* (digenic RP) [77,78]. However, the recent description of rod photoreceptor cell loss and outer segment abnormalities in mice with a targeted disruption of *Rom1* [79], rekindles the possibility that patients with *ROM1* alterations in the absence of *RDS* mutations may develop RP [80,81]. *RDS* mutations also have been identified in a variety of macular pattern dystrophies [82,83], and recent reviews more fully describe the complex phenotypic expressions in these cases [3,84].

Tetraspanins as a family form promiscuous associations with many different molecules and appear to function as facilitators of signaling pathways in a number of systems [85]. It is not known if peripherin/RDS and ROM1 have functions other than their described structural roles, but the intrafamilial heterogeneity of clinical symptoms in mutations of either *RDS* [86-91] or *ROM1* [81,92] provides genetic evidence of at least one unknown interacting protein. One potential candidate for these interactions is prominin like-1 (*PROM-1*), a five transmembrane domain protein that localizes to the evaginating discs of the rod outer segment, and which is mutated in rare cases of autosomal recessive retinal degeneration [93].

Photoreceptor cell transcription factors: The transcription factors NRL (*NRL*) and CRX (*CRX*), which synergistically control expression of photoreceptor cell specific genes [94], are known to be mutated in RP [95,96]. The mutations appear both to interfere with photoreceptor cell development and, much later in life, to cause photoreceptor cell degeneration [95-101]. Mutations in *CRX* have also been implicated as causative in some cases of cone-rod dystrophy [97,99] and Leber congenital amaurosis [95,102]. Recently, the allied disease known as enhanced S cone syndrome has been shown to be caused by mutations in the gene encoding the photoreceptor-specific nuclear receptor (*NR2E3*) [103], an orphan member of the nuclear receptor superfamily [104]. This disease also has clinical characteristics that indicate both a defect in retinal development, possibly in photoreceptor cell lineage decisions, associated with much later onset photoreceptor cell degeneration [103,105].

Catabolic functions in the retina: Although no defects in catabolism have been specifically noted in RP, several allied diseases and syndromic forms are due to failures to break down

metabolites in the retina. Sorsby's fundus dystrophy is due to mutations in the tissue inhibitor of metalloproteinases-3 gene (*TIMP-3*) [106]. This may lead to altered turnover of the extracellular matrix of the RPE basal lamina, Bruch's membrane. Among syndromic forms of RP, the products of cloned genes for two different Refsum diseases (phytanic acid storage diseases, *PEX1* and *PHYH*) [10] are thought to function in intracellular degradation pathways. Similarly, it has been speculated that the failure of ABCR leads to a build up of undigested vitamin A byproducts within the cells of the RPE in those diseases due to *ABCA4* mutations [51,56,57]. The phenotypic variability of the *ABCA4* mutations has been proposed to be related to the level of residual ABCR transport activity of the mutant proteins, and the consequently variable level of improperly catabolized substrates [7,57,68,69]. Many additional inborn errors of metabolism causing storage diseases of lipids, carbohydrates, and proteins that include retinal degenerations among their symptoms have also been described and characterized molecularly [15,107].

Mitochondrial genes: A final class of known genes that cause RP are involved in mitochondrial metabolism [108]. Mutations in the mitochondrial genome can cause several conditions in which RP-like symptoms are a feature, although the complexities of mitochondrial genetics lead to substantial variability in symptoms [109]. These diseases include Kearns-Sayre syndrome and a comorbidity of RP in association with deafness that is similar to one form of Usher syndrome [108,110]. The nuclear gene (*OAT*) for a clinically distinct allied disease, gyrate atrophy, also encodes an enzyme of mitochondrial metabolism, ornithine aminotransferase [111]

Genes of unknown function: Several of the identified RP genes encode products that lack described functions as yet. These include the genes for RP1 (*RP1*) [112-115], RP2 (*RP2*) [116], RP3 (retinitis pigmentosa GTPase regulator, *RPGR*) [117-119], RP12 (crumbs homologue 1, *CRB1*) [120], and RP14 (tubby-like protein 1, *TULP1*) [121-123]. The products of the genes for the allied diseases of Best macular dystrophy (vitelliform macular dystrophy, *VMD2*) [124,125], Doyme honeycomb retinal dystrophy (EGF-containing fibrillin-like extracellular matrix protein 1, *EFEMP1*) [126], and Leber congenital amaurosis type 4 (aryl-hydrocarbon interacting protein-like 1, *AIPL1*) [127], and of the Usher syndrome type 2A (*USH2A*) [128] also have unknown activities. Based on their primary sequence characteristics and/or clinical phenotypes, it seems possible to speculatively cluster some of these proteins into functionally related groups.

Interestingly, the predicted products of *RP2* [116], *RPGR* [129], *CRB1* [120], *TULP1* [130], and *AIPL1* [127], all seem to have features in common with proteins involved in intracellular trafficking. Similarly, the choroideremia (geranylgeranyl transferase Rab escort protein 1, *CHM*) [131,132] and Usher syndrome type 1B (an unusual myosin, type VIIA, *MYO7A*) [133] gene products may function in vesicular movement. A second potential grouping of these functionally cryptic proteins is in the metabolism of the extracellular matrix. The RP1 sequence has a series of hyaluronan binding sites [134], and the *EFEMP1* [126] and *USH2A* [128]

proteins both have sets of motifs common to extracellular matrix proteins. Finally, a number of these mutated proteins may have features in common with developmental signaling pathways. *RP1*, for example, has homology to the doublecortin gene (*DCX*) that is mutated in X-linked lissencephaly and double cortex syndrome [112,113], as well as a possible kinase domain [113]. Recently, *TULP1* has been proposed to encode a member of a unique class of transcription factors [135]. Consistent with this possible classification group, the genes for the allied disease congenital stationary night blindness 2 (an α subunit of an L-type voltage-gated calcium channel, *CACNA1F*) [136,137] and the gene for Alagille syndrome (a Notch ligand, jagged1, *JAG1*) [138,139] could also function in developmental signal transduction. Although the dual potential functions of RP1 and TULP1 may point towards interactions among these groupings, it remains to be seen whether these proteins will be assembled into functional cascades, as may be suggested by their sequence motifs, or whether they each act independently in retinal cell biology.

CONCLUSIONS

In this review, the clinical and electroretinographic fundamentals of retinitis pigmentosa were outlined, and the 19 known RP genes were grouped into functional categories. These genes include: *RHO*, *PDE6A*, *PDE6B*, *CNGA1*, *SAG*, *RPE65*, *RLBP1*, *ABCA4*, *RGR*, *RDS*, *ROM1*, *PROML1*, *NRL*, *CRX*, *RP1*, *RP2*, *RPGR*, *CRB1*, and *TULP1*. At least 17 additional uncharacterized RP genes are thought to exist by mapping data (summarized at RetNet). Genes mutated in several forms each of Leber congenital amaurosis, cone-rod dystrophy, cone dystrophy, and congenital stationary night blindness, and in a number of syndromes including forms of Bardet-Biedl, Alstrom, Refsum, and Usher syndromes are also uncharacterized (summarized at RetNet). It is important to remember that a number of the known RP genes have been found to be mutated in more than one clinical disease, as, for example, in the cases of *RHO*, *PDE6B*, *SAG*, *ABCA4*, *RDS*, and *CRX* discussed above. This raises the obvious possibility that some of the undescribed RP genes will actually be allelic with some of the undescribed genes for the allied diseases or syndromic forms of RP. It should also be noted that clinically classified diseases are now known to be caused by multiple independent genes, as in the cases of congenital stationary night blindness, cone-rod dystrophy, Leber congenital amaurosis, and classical RP itself. Even clinical subdivisions exhibit surprising genetic heterogeneity, as for example in the RP variant known as retinitis punctata albescens (Bothnia dystrophy), which has been found to be caused by mutations of the *RHO* [140], *RDS* [141], or *RLBP1* [142,143] genes. These observations imply that there may be a much greater extent of genetic complexity underlying RP and related ocular diseases than has even yet been appreciated.

No effective approach to prevention, stabilization, or reversal exists for the majority of RP cases. Additionally, in spite of the characterization of so many genes, genetic causes for the majority of cases have yet to be discovered. These facts, therefore, provide an impetus for ongoing research towards

two as yet elusive goals: the discovery of the underlying genetic causes of RP in most patients, and therapeutic intervention to halt or reverse the loss of photoreceptor cells. It is hoped that this review will provide some assistance in these twin quests.

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