Retinitis pigmentosa and allied diseases: numerous diseases, genes, and inheritance patterns

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Retinitis pigmentosa (RP) and allied diseases are heterogeneous clinically and genetically. Here we summarize the retinal cell types involved in these diseases, the large number of genes that cause them, and the variety of inheritance patterns that the affected families display. Special consideration is given to unusual inheritance patterns. The aggregate carrier frequency for recessive RP alleles may be as high as 10%.

INTRODUCTION

Inherited retinal degenerations and malfunctions are clinically and genetically heterogeneous. Many diseases in this group cause visual loss because of the premature death of the rod and cone photoreceptor cells. Retinitis pigmentosa (RP) is the most common retinal degeneration that is clearly hereditary. It affects about one in 5000 individuals worldwide (1). Patients with RP lose vision because of the death of both rods and cones throughout the retina (2–4). If the rods and cones (or perhaps other essential types of retinal neurons) are lost within the first years of life, or if they are already dead or nonfunctional at birth, the diagnosis becomes congenital retinal blindness, also referred to as Leber congenital amaurosis, especially if it is recessively inherited (5). Patients with macular degeneration lose the rods and cones of the central retina (the macula), while the photoreceptors in the retinal periphery are spared (6,7).

Although histopathologic studies of retinas from patients with color blindness have not been reported, clinical and genetic studies indicate that they have a degeneration, an aberrant spectral sensitivity, or a congenital absence of one or more of the three cone photoreceptor types (the long-wavelength, middle-wavelength, and short-wavelength cones, also termed the red, green, and blue cones) (8–16). In patients with a cone degeneration, all three types of cone photoreceptors die and the rod photoreceptors remain alive and functional (17). The end stage of cone degeneration is rod monochromacy, also called achromatopsia, in which vision is mediated exclusively by rod photoreceptors. Rod monochromacy can also be manifest from birth and can be due to congenitally absent or dysfunctional cone photoreceptors. There is no rod counterpart to cone degeneration; all rod photoreceptor degenerations have a secondary loss of cones and are categorized as RP. Patients with stationary night blindness have a full complement of rod and cone photoreceptors. In some of these patients, the rod photoreceptors are not sensitive to dim light or require an abnormally long time to adapt to dim light; in others, there is a likely defect in how photoreceptor signals are relayed to or processed by the inner retinal neurons in the bipolar cell layer (18).

Patients with hereditary optic atrophy have a reduced number of retinal ganglion cells (congenital optic atrophy) or a degeneration of these cells (acquired optic atrophy); other cells of the inner retina may also be reduced in number or dysfunctional in this condition. A small proportion of patients with hereditary retinal degenerations or malfunctions are considered to have ‘syndromes’ because they have associated extraocular disease (e.g., RP associated with hearing loss in Usher syndrome). When describing retinal degenerative diseases, the terms dystrophy and degeneration are used interchangeably (e.g., rod–cone dystrophy = rod–cone degeneration = retinitis pigmentosa; or, macular degeneration = macular dystrophy).

The boundaries separating some of the diagnostic categories are not distinct. For example, some patients with a rapid loss of cones and a slower loss of rods may be diagnosed with either cone–rod degeneration or retinitis pigmentosa depending on the judgment and bias of the clinician about the ratio of the rates of cone and rod loss that arbitrarily distinguish the two diagnoses. There are no characteristics that distinguish cone–rod degeneration and RP in their late stages when the retina is blind or nearly so. The diagnostic boundary separating severe RP from congenital retinal blindness is also blurred, since ophthalmologists are not in agreement about how early in life severe visual loss must occur for the diagnosis of congenital retinal blindness. Another example is stationary night blindness. Some patients with this condition lose a sufficient number of rod and/or cone photoreceptors late in life to prompt some clinicians to diagnose them as having RP or cone dystrophy (19,20). It should be noted that all humans lose photoreceptors with age. The average ‘wild-type’ 80-year-old has about 30%
fewer rods and cones than the average teenager (21,22). Electroretinogram amplitudes, which are objective, quantitative measures of the function of the photoreceptors, may decrease by 50% over the same time span (23,24), suggesting that the old photoreceptors that are still alive in an 80-year-old work less well than young photoreceptors. The boundary separating this rate of photoreceptor cell loss and dysfunction and the mild forms of RP is not defined.

**ALLELIC AND NONALLELIC HETEROGENEITY**

RP, most syndromic forms of RP, congenital retinal blindness, macular degeneration, cone degeneration, rod monochromacy, cone-rod degeneration, and stationary night blindness are all genetically heterogeneous. Only a few genes responsible for RP and its allied diseases were identified in the 1980s (e.g., the genes for color blindness in 1986 (8), and the genes for gyrate atrophy (25–27) and Kearns–Sayre syndrome (28–29) in 1988. In the last dozen years, however, the number of identified retinal disease genes has skyrocketed, with 75 identified genes reported as of January 2002. There are 45 additional genes that have been assigned to chromosomal regions through linkage studies, but which remain unidentified. Reviews of this set of genes and the diseases they cause have been published recently (1,30–36). Our tabulation of these genes is at http://eye-gene.meei.harvard.edu; an often cited database is http://www.sph.uth.tmc.edu/RetNet. Many investigators who search for and study retinal disease genes believe that there are many more of them still unidentified and unassigned. For example, in a recent commentary in Nature, Wright and van Heyningen speculated that the “total number is almost certainly two or three times the present figure” of known or mapped genes (37). The reason for this speculation is that it appears that most of the identified genes each account for disease in small numbers of patients. We estimate that roughly one-half to two-thirds of patients with RP have mutations in the previously identified RP genes, but this estimate is very rough because there are few studies that have exhaustively surveyed large numbers of patients to determine the prevalence of specific RP genes. (Our list of published studies that have calculated proportions of RP cases caused by mutations in selected genes can be found at http://eye-gene.meei.harvard.edu). It is reasonable to assume that the genes accounting for the highest proportions of cases would be preferentially already identified or mapped, since the ascertainment of families for linkage studies would by chance include the more frequent forms of the disease. If this assumption is correct, the remaining 33–50% of cases without mutations in identified or mapped genes might display an even greater degree of genetic heterogeneity than the cases where etiology has already been solved.

DIGENIC DIALLELIC INHERITANCE

The complementation test is often used to determine whether a recessively inherited phenotype is genetically heterogeneous. If two parents with the same recessive phenotype produce unaffected offspring, then one typically concludes that the parents differ in the genes causing their phenotype. All offspring of such a mating are obligate heterozygotes, carrying one mutant and one wild-type allele at each of the two loci. The two loci are said to complement each other, or to exhibit nonallelic complementation. Nonallelic noncomplementation, also called unlinked noncomplementation, describes the exceptional circumstance in which the double heterozygote offspring are affected. Phenotypes exhibiting nonallelic noncomplementation have been documented in nematodes (39), yeast (40), fruit flies (41), and mice (42).

The test is easily applied to non-human organisms which, in a laboratory setting, have little choice as to their mates. In the study of human diseases, it usually depends on fortuitously observed families in which both parents have the same recessively inherited trait. Although families in which both parents have a hereditary retinal degeneration are infrequent, some have been ascertained. For example, the unaffected offspring of a couple with Leber congenital amaurosis provided evidence that more than one gene could cause this disease (i.e., nonallelic complementation) prior to molecular genetic analysis (43).

Since the complementation test involves the mating of two affected individuals, geneticists confined their consideration of
this phenomenon to such families. This tunnel vision caused investigators to overlook the possibility that the inheritance of diseases produced by nonallelic noncomplementation could approximate recessive or dominant inheritance patterns. Affected individuals would be heterozygotes for mutations at two unlinked genes (i.e., double heterozygotes). As illustrated in the schematic pedigree in Figure 1, a digenic-diallelic disease would begin in the offspring of unaffected parents, each of whom would carry one of the two mutations. One out of four offspring would inherit both mutant alleles; only these double heterozygotes would be affected. Thus, the first generation of affected individuals mimics a recessive disease. Like a dominant disease, however, the affected double heterozygotes are able to transmit both mutations and hence the disease to their offspring. The transmission ratio would be only 1 in 4, less than the ratio of 1 in 2 for a dominant disease. The term ‘digenic-diallelic inheritance’ can be used to describe this sort of inheritance.

The first documentation of digenic-diallelic inheritance in a human disease came from studies of the RDS and ROM1 genes in a handful of families with RP. In these families, all affected individuals were double heterozygotes, carrying a likely null mutation in the ROM1 gene on chromosome 11q and a missense mutation in the RDS gene on chromosome 6p (44,45). Relatives who carried only one of these mutations were unaffected. Mice with rds and rom1

![Figure 1. Schematic pedigrees demonstrating dominant, dominant with reduced penetrance, digenic diallelic, recessive, and digenic-triallelic diseases. All of these inheritance patterns have been observed in families with RP. Affected individuals are represented by filled circles and squares. A dot in an individual's symbol indicates that he or she is an unaffected carrier of a dominant RP allele. The genotypes are under each family member’s symbol. A, a1, a2, B, and b all designate mutant alleles, with the A, a1, and a2 alleles found at one locus and the B and b alleles at a second locus not linked to the first. + designates a wild-type allele. In the family with autosomal dominant disease with reduced penetrance, +1 and +2 designate isoalleles, with the isoallele +2 preventing the expression of RP in a patient with the mutant A allele in trans (a situation presumed to be present in an unaffected carrier of an RP11 mutation). Note that the digenic diallelic disease mimics a recessive pedigree in the first affected generation and mimics a dominant disease with a reduced transmission ratio in subsequent generations. Digenic-triallelic disease differs from autosomal recessive disease by its lower recurrence risk.](image-url)
genotypes similar to those found in these families have corresponding phenotypes (46). Most of the genes from lower animals that fail to complement each other encode proteins that interact (39–41). This is also true for the RDS and ROM1 genes. Both the RDS and the ROM1 proteins are exclusively found in the rims of the photoreceptor discs (47–52), and they form homodimers that interact noncovalently to produce a tetrameric complex with two RDS molecules and two ROM1 molecules (53–55). This complex is necessary for the structure of the disks in the rod and cone outer segments; without it the disks do not form and the photoreceptors degenerate (56–58). The RDS missense mutation that is found in all recognized RDS/ROM1 digenic families affects an amino acid in a large intradiscal loop that is important for the assembly of this complex (55,59). The mutant can form RDS/RDS dimers, but these mutant dimers do not readily form a tetrameric complex with a ROM1/ROM1 dimer. Disease in double heterozygotes with the RDS missense change and a ROM1 null allele is presumably due to the greatly decreased amounts of functional tetramers. Single heterozygotes with only the RDS or only the ROM1 mutation apparently form sufficient tetramer to maintain photoreceptor disk structure and viability.

There are many known RP genes whose gene products interact with the products of other RP genes. It is possible that double heterozygotes with mutations in other combinations of these genes, besides RDS and ROM1, might produce a retinal degeneration, but these combinations remain to be identified.

DIGENIC TRIALLELIC INHERITANCE

Up to 5% of patients with RP have a syndromic variant called Bardet-Biedl syndrome (BBS) in which the retinal degeneration is co-inherited with polydactyly, short stature, truncal obesity, hypogonadism, mental retardation, and kidney disease (60,61). Until recently, BBS was considered to always exhibit an autosomal recessive mode of inheritance (62–65). Linkage studies and gene identifications indicated that mutations at any of at least six different genes could produce the disease, but, in any given family, it was presumed that only one of these six loci was involved. However, families were recently discovered in which affected individuals had mutations affecting both alleles at one BBS locus (usually BBS2) and one allele at a second BBS locus (usually BBS6) (66). The requirement for all three mutant alleles was demonstrated by one of these families in which there was an affected sibling with two BBS2 mutant alleles and one BBS6 mutant allele and an unaffected sibling with only the two BBS2 mutations. A representation of the genotypes and phenotypes in a hypothetical family with digenic triallelic disease is shown in Figure 1.

Of the six BBS loci assigned through linkage studies, only three have been identified (63), including BBS2 and BBS6 (64,65). The protein product of the BBS6 locus appears to be a chaperone protein (63,67), but the function of the protein produced by BBS2 remains obscure (65). The identification of the remaining BBS genes and the elucidation of the function of all of the BBS proteins may help us to understand the mechanisms that result in this interesting mode of inheritance.

Digenic inheritance should probably be limited to instances where double heterozygotes or triple or quadruple carriers of mutations in a total of two loci have a phenotype not exhibited by relatives with a lesser number of mutant alleles. The terms diallelic, triallelic, and tetra-allelic could be used to signify the number of mutant alleles in the two genes necessary to produce the phenotype. Digenic inheritance could explain the occasional family in which two parents with apparently recessive deafness have both affected and unaffected offspring (68). A less speculative example of nonocular disease likely due to a digenic triallelic genotype is junctional epidermolysis bullosa due to mutations in COL17A1 and one mutation in LAMB3 (69). A mouse model of spina bifida has been described with digenic triallelic inheritance (70).

We would recommend that the term digenic not be used for phenotypes that are clearly primarily caused by mutations in a single gene and that become more severe when a mutation in an additional gene is also present. Instead, the additional gene is better understood as a modifier gene. For example, the presence of a mutation in the myosin VIIA gene (a recessive cause of RP with congenital hearing loss and vestibular ataxia) correlates with more severe deafness in a patient with Usher syndrome type III (recessive RP associated with gradually worsening hearing loss) caused by a distinct gene on another chromosome (71); the myosin VIIA mutation should be considered a modifier of the Usher type III gene. Similarly, the presence of an ABCA4 allele is associated with more severe macular degeneration caused primarily by the dominant Stargardt-like gene on chromosome 6 (72). Additional reports of digenic diseases that are probably more correctly considered examples of modifier alleles are open angle glaucoma caused by dominant mutations in MYOC and made more severe by a mutant allele in the CYP1B1 gene (73), and nonsyndromic deafness, which is more severe in patients with the combination of mutations in two genes compared to those with mutations in only one (74).

DOMINANT RETINITIS PIGMENTOSA WITH REDUCED PENETRANCE

Obscure environmental and genetic factors must be invoked to explain the variation in the severity of RP among patients who have the same dominant mutation or the same recessive mutations. The range in severity can be large. For example, some patients with dominant RP due to the rhodopsin mutation Pro23His can have over 100 times more photoreceptor function than comparably aged patients with the same mutation (75). A notable example is provided by the family with dominant RP caused by a gene linked to chromosome 7p in which some adult carriers can be asymptomatic while others can have severely constricted visual fields (76,77). While investigators have documented a wide range in the severity of RP caused by mutations in these and other RP genes, the causative mutations all appear to be completely penetrant. Even the most mildly affected patients have signs of retinal degeneration detected through funduscopy or electroretinography (ERGs), usually by six years of age (78). However, exceptional families with dominant RP exhibit incomplete penetrance.
In these families, some obligate carriers remain unaffected even after many years of follow-up (79–85).

Studies of families with dominant RP with reduced penetrance revealed that all exhibited linkage between the responsible gene, called RP11, and markers within chromosome 19q13.4 (81,83,86). Furthermore, the same linkage studies provided strong evidence that a single locus determines whether or not carriers of an RP11 mutation would develop RP, and that this ‘penetrance locus’ was either closely linked to RP11 or was RP11 itself (86). The evidence came primarily from sibships with both affected and unaffected carriers. In each of these sibships, the unaffected carrier siblings all inherited the same wild-type RP11 allele from their noncarrier parent and the affected siblings all inherited the other noncarrier RP11 allele from the unaffected parent (based on an examination of polymorphic markers closely linked to the RP11 locus) (86). In other words, there are wild-type alleles, properly called isoalleles, at the RP11 locus or a closely linked locus which by themselves produce no observed phenotype, but, when in trans with a dominant mutation in RP11, permit or inhibit the pathogenicity of that mutation (Fig. 1). There is precedent for such a pattern in a disease not involving the retina. Individuals carrying a dominant mutation in the alpha-spectrin locus might or might not develop hemolytic anemia (the result of abnormally shaped red blood cells) depending on the nature of the wild-type alpha-spectrin allele that they carry in trans (87,88). The isoalleles differ in the amount of wild-type alpha-spectrin that they produce. High expressing isoalleles apparently produce sufficient amounts of this cytoskeletal protein to dilute the effect of a mutant version in trans.

The RP11 gene has been recently shown to encode an ubiquitously expressed protein that forms an essential part of the spliceosome (89). Still a mystery is how defects in this mRNA splicing factor, called PRPF31, cause a disease confined to the retina. Some of the mutations appear to be null alleles, so it appears that the retina is especially sensitive to the reduced levels of this splicing factor that are presumably present in affected patients. Additional experiments are necessary to determine whether isoalleles at the PRPF31 locus exist and whether they vary in their ability to produce wild-type PRPF31. If the penetrance locus is not RP11 itself, the search must begin for this locus among the neighbors of RP11 on chromosome 19q.

**UNIPARENTAL DISOMIES**

Perhaps as many as one in 600 individuals inherit two chromosomes of a given chromosome pair from one parent and no copy from the other (90). This unusual mode of inheritance is termed uniparental disomy, and it is the result of abnormal events during either meiosis, fertilization, or the early stages of embryonic development (reviewed by Kotzot (91)). If the uniparentally inherited chromosome pair is the same as the pair present in the donor parent, this situation is termed uniparental heterodisomy. In contrast, if the uniparentally inherited pair is originated from the duplication of only one parental chromosome, the individual is homoallelic for all loci on that chromosome, and the condition is termed uniparental isodisomy. Uniparental, isodisomic chromosomes in a pair can have regions that are isodisomic if meiotic recombination events occurred after the abnormal segregation of the involved chromosome pair.

Uniparental isodisomy can reveal recessive alleles that may be present in the retained chromosome, since the isodisomy would bring the recessive allele to homozygosity. One isodisomic patient with recessive RP due to a mutation in the MERTK gene (chromosome 2) and another with a mutation in the RPE65 gene (chromosome 1) have been described in a total of three reports (92–94). Our group has identified a patient with recessive RP who was isodisomic for a region of chromosome 1q including a mutant allele at the USH2A locus (95). A report of a patient with rod monochromacy who was isodisomic for chromosome 14q has been used as evidence that a recessive gene for that condition is on that chromosome (96), but that gene remains unidentifed and additional evidence supporting the existence of this gene has yet to be obtained.

There are too few reported cases of RP associated with uniparental isodisomy to know for certain the frequency of this combination. However, a rough estimate can be calculated based on Engel’s estimate of the frequency of uniparental disomy (1 in 600) (90) and an assumed frequency of 10% for carriers of a recessive RP allele (the latter estimate is explained in the last section of this paper). Since there are 22 autosomes, the chance that the affected chromosome in a patient with isodisomy carries a recessive RP allele is roughly 1/22 × 1/10 = 1/220. (The factor 1/2 is included because a carrier has the mutant allele on only one of the two chromosome homologues). If one in 600 individuals have uniparental disomy, and if at least half of these are isodisomic or are heterodisomic with regions of isodisomy spanning the mutant locus, then the prevalence of uniparental disomy and recessive RP would be 1/600 × 1/220 = 1/120000. This is close to 2% of the prevalence of isolate RP (1/528000). Although the assumptions made here might overstate the actual percentage, the calculations nevertheless suggest that this phenomenon must be considered in the genetic evaluation and probably the genetic counseling of isolate cases of RP.

**SOMATIC MOSAICISM**

Most studies of the prevalence of RP have found a large number of isolate cases. These are presumed to represent cases of recessive RP or X-linked RP who by chance have no affected siblings, or, alternatively, represent cases with newly arising mutations. However, the large proportion of isolate cases leaves the possibility open that some RP alleles might be embryonic lethals and thus are only observed in mosaics (97). To date, there is no proven case of RP due to mosaicism for a somatically arising mutation. All patients with paravenous RP are isolate cases, and perhaps this rare form of RP, in which degeneration is mainly confined to the retina around the major retinal veins (98), is due to somatic mutations in an as yet unidentified gene. Unilateral RP may be another possible example of somatic mosaicism since it also is almost always nonfamilial (98). Sector RP, in which only a portion of the retina appears to degenerate (99), is unlikely due to mosaicism since the disease is bilateral and symmetric (i.e., the corresponding region of the retina in both eyes is involved).
Female carriers of mutations in X-linked RP genes are all mosaics because of differential X chromosome inactivation (Lyonization). They usually have fundus features and/or electroretinographic abnormalities that indicate a modest loss of photoreceptors (100,101). However, some carrier females exhibit signs and symptoms of retinal degeneration that is presumably due to unfavorable Lyonization that inactivates the normal X chromosome in the majority of their retinal cells. The signs and symptoms can be so severe that some clinicians will entertain the diagnosis of RP and consider the family to have an X-linked dominant form of RP. However, in most such families, the carrier females will have disease far less severe than their affected male relatives, so that the designation of X-linked dominant inheritance is probably not accurate.

**NUMEROUS GENES IMPLY NUMEROUS CARRIERS**

The high number of recessive genes that can cause RP must be taken into account when estimating the frequency of unaffected carriers of one or more recessive mutations. The frequency of recessive RP is roughly one in 6000 (102,103). If all cases of recessive RP were caused by mutations in the same gene, the carrier frequency is simply calculated as $(1/6000)^{0.5}$, or about one in 80. However, if there were two recessive RP genes each contributing to half of the cases, the prevalence of each one would be one in 12000, and the carrier frequency of each would be one in 109, for a combined carrier frequency of about one in 55. Figure 2 illustrates the results of similar calculations and shows how the aggregate carrier frequency increases as the number of recessive RP genes increases. Although the exact number of recessive RP genes is still not known, at least 45 have been identified or implicated by linkage studies, and it is likely that many more exist. If more than 67 such genes exist, the aggregate carrier frequency becomes greater than 10%. This is higher than the carrier frequency for cystic fibrosis, a recessive disease often cited as having one of the highest carrier frequencies among Caucasians. The actual aggregate carrier frequency would be lower if some genes account for a higher proportion of cases than others and if there were numerous examples of digenic diallelic RP. It would be higher if one includes other recessively inherited photoreceptor diseases such as cone-rod degeneration or macular degeneration. The high carrier frequency explains the many instances where patients with a retinal disease that is clearly the result of a mutation in one gene are found also to carry a mutation in another RP gene, or where unaffected control individuals are found to carry recessive RP alleles (104-107).

It should be noted that for the genetic counseling of an individual patient, it is not the aggregate frequency but the individual gene carrier frequency that is important. Although the aggregate carrier frequency increases with an increase in the number of RP genes, the carrier frequency for any single gene decreases (Fig. 2). For example, if there were 67 recessive RP genes of equal frequencies, the aggregate carrier frequency would be 10%, but the carrier frequency for any given one of the 67 genes would be only one in 634, or 0.0016. Thus, the chance that a known obligate carrier (e.g., the offspring of a patient with recessive RP) will have a spouse who is also a
carrier (with a resulting one in four chance of each of their children being affected) is much lower than would be expected if there were only one or a few recessive RP genes.

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