ARTICLE

Molecular genetics of human retinal dystrophies

CHRIS F. INGLEHEARN

Abstract

Retinal dystrophies are a heterogeneous group of diseases in which the retina degenerates, leading to either partial or complete blindness. The severe and clearly hereditary forms, retinitis pigmentosa (RP) and various macular degenerations, affect approximately 1 in 3000 people, but many more suffer from aging macular dystrophy in later life. Patients with RP present with narrowing visual fields and night blindness, while those with diseases of the macula lose central vision first. Even before the advent of molecular genetics it was evident that these were heterogeneous disorders, with wide variation in severity, mode of inheritance and phenotype. However, with the widespread application of linkage analysis and mutation detection techniques, a complex underlying pathology has now been revealed. In total, 66 distinct non-overlapping genes or gene loci have been implicated in the various forms of retinal dystrophy, with more being reported regularly in the literature. Within the category of non-syndromic RP alone there are at least 22 genes (and probably many more) involved, with further allelic heterogeneity arising from different mutations in the same gene. This complexity presents a problem for those involved in counselling patients, and also compounds the search for therapies. Nevertheless, several lines of research raise the hope of generic treatments applicable to all such patients, while the greater understanding of normal visual function that arises from genetic studies may open up new avenues for therapy.

Key words Macular dystrophy, Retina, Retinal dystrophy, Retinitis pigmentosa

Background

In 1857, shortly after the invention of the ophthalmoscope, the German physician Donders described 'bone spicule' pigmentation in the retina in some forms of blindness.[1] The pigmentary deposits he observed are thought to result either from migration of retinal pigment epithelial (RPE) cells into a degenerating retina, or from macrophages that incorporate the pigment on their way from the choriocapillaris into the diseased retina. To describe what he saw, Donders coined the term retinitis pigmentosa (RP), technically a misnomer since the primary defect in RP is not inflammatory, but the name has stuck and is now widely used. In modern usage, the term applies only to those retinal dystrophies that begin in the peripheral retina, causing night blindness and loss of visual fields, only later progressing to the macula. RP affects approximately 1 in 4000 people, and is the commonest retinal dystrophy.[2,3]

Figures for the frequency of macular and cone–rod dystrophies, which begin in the central retina, are less easy to come by. Those inherited as simple mendelian disorders are less common than RP, but in an aging western population, age-related macular dystrophy (AMD) is increasing in prevalence and is clearly at least in part an inherited disease. Together, hereditary retinal dystrophies accounted for 11.5% of those registered blind under the age of 65 years in England and Wales in a recent survey.[4]

Genetic heterogeneity

It was evident from family studies carried out in the early part of this century that retinal degenerations could be inherited in dominant, recessive and X-linked modes. When molecular genetic technology was applied to these diseases in the early 1980s it rapidly became obvious that even within inheritance classes there was still further genetic heterogeneity. We now know that dominant retinitis pigmentosa (adRP) results from mutations in at least ten mapped loci, X-linked RP (x1RP) from mutations in at least three loci and recessive RP (arRP) from a further nine loci. Usher's syndrome maps to at least seven different loci, Bardet–Biedl syndrome to four and Stargardt's disease (both dominant and recessive) to three; there are also at least 15 different non-syndromic forms of central retinal dystrophies. An assortment of other syndromes and phenotypes brings the current total to at least 66 non-overlapping retinal dystrophy loci, of

C.F. Inglehearn ✉
Molecular Medicine Unit
Clinical Sciences Building
St James's University Hospital
Leeds LS9 7TF, UK
Tel: +44(0)113 206 5698
e-mail: cinglehe@hgmp.mrc.ac.uk

Table 1. *Retinal dystrophy loci, listed by chromosome*

Phenotype	Locus/gene	Chromosomal localisation	Reference
Ocular albinism	OA1 (g)	Xp22.3–p22.2	5
Juvenile retinoschisis	XLRS1 (g)	Xp22.2	6
Cone–rod degeneration	RP15	[Xp22.13–p22.11	7
Retinitis pigmentosa	RP6	[Xp21	8
Retinitis pigmentosa/CSNB	RPGR (g)	Xp21.1	9, 10
CSNB	CSNB4	[Xp11.4	11
Cone dystrophy	COD1	[Xp11.3	12
Optic atrophy	XLOPT	Xp11.4–p11.2	13
Norrie disease/exudative vitreoretinopathy	NDP/EVR2 (g)	Xp11.4	14, 15
Retinitis pigmentosa	RP2	[Xp11.23	16
CSNB	CSNB1/2	[Xp11	17, 18
Aland Island eye disease	AIED/OA2	[Xp11	19
Choroideraemia	REP1 (g)	Xq21	20
Albinism–deafness	ADFN	Xq26.3–p27.1	21
Cone dystrophy	COD2	Xq27	22
Blue cone monochromacy/central retinal dystrophy	GCP/RCP (g)	Xq28	23
Leber's amaurosis	RPE65 (g)	1p31–21	24, 25
ar Stargardt's disease/age-related macular dystrophy/ ar retinitis pigmentosa	ABCR (g)	1p21–13	26, 27, 28
ad Retinitis pigmentosa	RP18	1cen	29
ar Retinitis pigmentosa	RP12	1q31–32.1	30
Usher syndrome type 2	USH2A	1q41	31
ad drusen (Doyne's malattia leventinese)	DHRD/MLTV	2p16	32, 33
ar Achromatopsia	RMCH	2p11–q12	34
Oguchi disease (ar CSNB)	SAG (g)	2q37	35
ad CSNB (Nougaret night blindness)	GNAT1 (g)	3p21	36
ad cerebellar ataxia/macular dystrophy	SCA7 (g)	3p21–p12	37
Bardet–Biedl syndrome	BBS3	3p13–p12	38
ad/ar Retinitis pigmentosa/ad CSNB	RHO (g)	3q21–24	39, 40
Usher syndrome type 3	USH3	3q21–24	41
ad Optic atrophy	OPA1	3q28–29	42
ar Retinitis pigmentosa/ad CSNB	PDEB (g)	4p16.3	43
ar Retinitis pigmentosa	CNGC (g)	4p12–cen	44
Abetalipoproteinaemia	MTP (g)	4q22–q24	45
Wagner disease/erosive vitreoretinopathy		5q13–q14	46
ar Retinitis pigmentosa	PDEA (g)	5q31.2–q34	47
ar Retinitis pigmentosa	RP14	6p21	48
ad Digenic Retinitis pigmentosa/ad macular dystrophy/ ad pattern dystrophy	RDS/peripherin (g)	6p12	49, 50, 51, 52, 53, 54
ad Stargardt's disease	STGD3	6q11–q15	55
North Carolina macular dystrophy/progressive bifocal chorioretinal atrophy	MCDR1/PBRCA	6q13–q21	56, 57
ad Cystoid macular dystrophy	DCMD	7p15–p21	58
ad Retinitis pigmentosa	RP9	7p14	59
ad Retinitis pigmentosa	RP10	7q31–q35	60
ad Retinitis pigmentosa	RP1	8q11	61
ar Oculocutaneous albinism OCA3	TYRP (g)	9p23	62
ad Retinitis pigmentosa/deafness	RP8/21	9q34	63
Usher syndrome	USH1D	10p24–p21	64
Refsum disease	PAHX/PHYH (g)	10p15–p12	65, 66
Gyrate atrophy	OAT (g)	10q26	67
ad Atrophia areata	AA	[11p15	68
Usher syndrome type 1	USH1C	[11p15.1–p14	69
ad Digenic retinitis pigmentosa	ROM1 (g)	11q13	70, 54
Best vitelliform macular dystrophy	VMD2	11q13	71
Bardet–Biedl syndrome	BBS1	[11q13	72
ad Exudative vitreoretinopathy	EVR1	[11q13–23	73
ad Inflammatory vitreoretinopathy	VRN1	[11q13	74
Usher syndrome type 1	MYO7A (g)	11q13	75
Oculocutaneous albinism OCA1	TYR (g)	11q14–21	76
Oguchi disease (ar CSNB)	RHOK (g)	[13q34	77
ad Stargardt's disease	STGD2	[13q34	78

Table 1. – *continued*

Phenotype	Locus/gene	Chromosomal localisation	Reference
Usher syndrome type 1	USH1A	14q32	79
ar Oculocutaneous albinism OCA2	P (g)	15q11.2–q12	80
Bardet–Biedl syndrome	BBS4	15q22.3–q23	81
ar Retinitis pigmentosa	CRALBP (g)	15q26	82
ar Retinitis pigmentosa		16p12–q13	83
Bardet–Biedl syndrome	BBS2	16q21	84
ad Retinitis pigmentosa	RP13	17p13.4	85
Central areolar choroidal dystrophy	CACD	[17p13	86
ad Cone/cone–rod dystrophy	CORD5/6	[17p13–12	87, 88
Leber's amaurosis	RETGC (g)	[17p13.1	89
ad Retinitis pigmentosa	RP17	17q22–24	90
ar Optic atrophy/3-methylglutaconic aciduria		19q13.2–13.3	91
ad Cone–rod dystrophy	CORD2	19q13.2	92
ad Retinitis pigmentosa	RP11	19q13.4	93
Alagille syndrome	JAG1 (g)	20p11–p12	94
Usher syndrome type 1	USH1I	21q21	95
Sorsby's fundus dystrophy	TIMP3 (g)	22q12.1–q13.2	96

Gene and locus symbols given are the standard nomenclature adopted by the HUGO/GDB Nomenclature Committee, and can be used to search the GDB or OMIM databases. Loci marked with a (g) are those for which the genes involved have been identified. Adjacent loci with bracketed localisations are potentially allelic mutations in the same gene, since the genetic intervals for each overlap. The letters 'ar' and 'ad' stand for autosomal recessive and autosomal dominant. Other abbreviations are as defined in the text.

which 29 are known genes. These are listed by chromosome in Table 1.

X-linked retinitis pigmentosa

Early RP research focused on large, clearly X-linked families, since mode of inheritance provided a clue as to which chromosome to study. Females in such pedigrees are sometimes affected with varying degrees of severity, indicating carrier status, but males are consistently severely affected and never pass the defect on to their male children. Bhattacharya and colleagues[16] were the first to apply molecular genetic techniques to RP, with the discovery of linkage to the restriction fragment length polymorphism marker L1.28, on Xp.11. This locus was assigned the name RP2, and soon after, a second xlRP locus, RP3, was placed distal to RP2 on Xp21.[8] The RP2 gene has not been identified, but Meindl and co-workers[9] recently reported the cloning of the RPGR gene, which is in the RP3 region and is mutated in some xlRP families and patients. The function of this gene remains to be elucidated, but the apparent lack of mutations in some RP3 families has already led to speculation of a second RP gene nearby, or so-called micro-heterogeneity. In addition, multipoint analysis of a large number of xlRP families implicated a third locus, RP6, still more distally on Xp.[8] This locus overlaps with the X-linked dominant cone rod dystrophy locus RP15,[7] implicating at least one more xlRP gene. This picture is further complicated by the existence of a range of other X-linked retinal phenotypes, including cone dystrophy, congenital stationary night blindness (CSNB), Norrie's disease and Aland Island eye disease, all with loci overlapping the xlRP intervals and which might or might not be allelic with them (see below).

Autosomal dominant RP

As genetic maps improved, the first dominant locus was identified on chromosome 3q21–24.[97] Dryja and colleagues[39] then quickly identified mutations in the rhodopsin gene in adRP patients. This gene encodes the visual pigment at the top of the rod phototransduction cascade, which is in the region pinpointed by the initial linkage result. In all there have now been over 90 such mutations reported.[98] Most cause dominant RP, but two recessive mutations and two mutations causing dominant CSNB have also been described. In general, dominant rhodopsin-RP patients fall either into the D-type/type 1 category described by Massof and Finkelstein[99] and Lyness *et al.*[100] or have sector RP as described by Moore *et al.*[101] This latter category consists mainly of mutations in the first exon of the gene and therefore at the amino-terminus of the protein or in the first transmembrane domain. As yet, sector RP has not been assigned to any other locus, and therefore appears to be uniquely associated with mutations in rhodopsin.

It was soon evident that rhodopsin-RP did not account for all adRP, however, and in 1991 two groups reported mutations in dominant RP patients in the peripherin/RDS gene on chromosome 6p12.[49,50] This protein is expressed in both rods and cones and is thought to play a structural role in maintaining the shape of rod discs and cone lamelli. Its involvement in inherited retinal dystrophy was first established when it was found to be the gene mutated in the mouse model Retinal Degeneration Slow (RDS). Further studies have revealed over 40 mutations in retinal degeneration patients, but interestingly some of these are in patients with macular, cone–rod and pattern dystrophies as well as RP. Most of the known pathogenic mutations in the peripherin/RDS protein are in the large intradiscal loop,

Table 2. *Dominant retinitis pigmentosa: phenotypes and frequencies*

Locus	Penetrance	Age at onset	Phenotype	Frequency
RP18;1cen	100%	1st decade	Type 1/D	1 = 3%
RHO;3q21–24	100%	1st decade	Type 1/D	16 = 50%
RDS;6p12	Variable	Variable	Many	1 = 3%
RP9;7p14	90%	Variable	Type 2/R	1 = 3%
RP10;7q31–35	100%	2nd–3rd decade		1 = 3%
RP1;8q11	95%	Variable	Type 2/R	1 = 3%
ROM1;11q13	Not known	Variable		0
RP13;17p13	100%	1st decade		1 = 3%
RP17;17q22–24	100%	3rd decade		1 = 3%
RP11;19q13.4	65%	2nd–3rd decade	Type 2/D	5 = 16%
Unlinked to known loci				4 = 13%
Total families studied				32

which is thought to function in binding together opposite sides of the rod disc and cone lamella membranes. These mutations and their associated phenotypes are reviewed by Keen and Inglehearn.[107]

In addition, seven adRP loci have been implicated by linkage analysis only,[29,59,60,61,85,90,92] and for each of these the gene remains to be identified. Without the gene, it is not possible to carry out comprehensive mutation screening, which makes it impossible to estimate the frequency and hence clinical significance of these loci. My colleagues and I therefore carried out a linkage-based screen of 20 large (>11 meioses) adRP pedigrees. Linkage has the advantage that it cannot miss mutations in the way that mutation screening techniques can, and use of large, clearly dominant families avoids the ambiguity in a clinic-based patient series of diagnoses based on a verbally ascertained family history. In this screen we found that rhodopsin-RP may account for as much as 50% of adRP – higher than previous estimates – and that RP11 on 19q is the second most common locus.[103] By analysing additional families and by lowering the criteria for inclusion of a family to only eight meioses, enough to obtain a confirmatory lod score of over 2 at a known locus, this series has been expanded to 32 adRP families. The most recent figures, which remain consistent with the conclusions above, are shown in Table 2.

Autosomal recessive RP

Recessive RP was the last category to be studied, because in most cases there is little or no family structure to provide clues as to the whereabouts of the mutation. This problem has been circumvented in two ways. The first is the candidate gene approach, which has become feasible with the advent of mutation screening by the polymerase chain reaction (PCR). With this approach Dryja and colleagues implicated four different components of the visual transduction cascade in recessive RP causation. These are rhodopsin,[40] two subunits of cGMP phosphodiesterase[43,47] and the cGMP-gated ion channel protein CNGC.[44] Mutation screening indicates that each of these loci accounts for less than 5% of all simplex and known recessive RP cases.

The second approach is to identify large pedigrees from social cultures where inbreeding is the norm, and in which a recessive defect is segregating. This approach identified an arRP locus on 1q in a Dutch family[30] and another on 6p in a Dominican family.[48] A third locus on 1p, mapped in a Spanish consanguineous family, overlaps with the locus for Stargardt's macular dystrophy and may be allelic with it.[104] In addition, recent studies of inbred recessive RP pedigrees from India have implicated the RPE65 gene on 1p[24,25] and the CRALBP gene on 15q26,[82] as well as identifying a further as yet uncharacterised locus on 16p.[83] These results are of particular note since both RPE65 and CRALBP are expressed primarily in the retinal pigment epithelium, not the retina. Degeneration in these cases appears to result from an inadequate supply of fat-soluble retinoids to the retina due to mutations in binding proteins that would normally allow such compounds to be stored and transported around the body. In each of these cases it is impossible to estimate the frequency of mutations in these genes in any given population, but it seems likely that many more recessive RP loci remain to be found.

Digenic RP

In 1994 Kajawara and colleagues[54] reported RP patients who were compound heterozygotes for certain specific mutations in two different genes: the peripherin/RDS gene on chromosome 6p and the ROM1 gene on 11q. The ROM1 protein (Rod Outer segment Membrane protein 1) is homologous to peripherin/RDS and is thought to have a similar structural role, perhaps forming a functional dimer complex with peripherin/RDS. Parents of these patients were carriers for either the ROM1 or the peripherin/RDS mutations but had no symptoms. In the first generation the disease mimics recessive inheritance, with 25% of children affected. However, unlike true recessive disease there is then a recurrent risk to the next generation, again of 25%. Other peripherin/RDS mutations have of course been associated with a range of dominant conditions, as described above. Similarly ROM1 mutations have also been found, in the absence of peripherin/RDS mutations, in small apparently dominant pedigrees and in sporadic cases.[70] The observation of digenic retinal degeneration may imply

that a proportion of RP is more complex in origin, resulting from unfavourable combinations of alleles at many loci rather than deriving from relatively simple mendelian single gene defects.

Congenital stationary night blindness

CSNB patients have non-progressive night blindness, often associated with myopia and decreased visual acuity. To date there are three autosomal dominant, two autosomal recessive and two X-linked loci. Recessive CSNB, known as Oguchi disease, results from mutations in S-arrestin[35] and rhodopsin kinase,[77] both of which function to restore the resting phase in rods after response to light. Dominant CSNB is associated with certain mutations in rhodopsin, while other rhodopsin mutations cause dominant and recessive RP, as described above.[98] Dominant CSNB also results from mutations in the beta subunit of phosphodiesterase (PDEB),[36,105] another locus previously implicated in RP, and in the alpha subunit of transducin. One X-linked form of CSNB derives from certain mutations in the RP3 gene RPGR,[10] while another X-linked CSNB locus is in an interval overlapping that of the RP2 locus.[17,18] The co-incidence of CSNB and RP in at least four loci suggests that CSNB is a mild, non-progressive version of RP, where rod function is abnormal but the retina does not degenerate.

Syndromic RP

The two most well studied syndromes involving RP, both recessive, are Usher syndrome and Bardet–Biedl syndrome. Three phenotypic variants of Usher syndrome (RP and deafness) are defined according to severity of hearing loss and the degree of vestibular involvement leading to balance problems. Type 1, with profound hearing loss and vestibular dysfunction, is genetically heterogenous, with loci on chromosomes 14 (Ush1A),[79] 11q (Ush1B),[75] 11p (Ush1C),[69] 10q (Ush1D)[64] and 21q (Ush1E).[95] Type I accounts for between 60% and 90% of all cases of Usher syndrome, and Ush1B mutations are thought to cause around 75% of type I Usher syndrome,[106] so the 11q locus is almost certainly the most clinically significant. The Ush1B gene has been identified as myosin VIIA, which has also been implicated in non-syndromic deafness.[75,107] Usher type 2 patients present with RP, moderate hearing loss and normal vestibular function, which maps to chromosome 1q (Ush2A).[31] In type 3 Usher syndrome, hearing loss and balance problems, like the RP, are progressive. This phenotype maps to chromosome 3q (Ush3).[41]

In contrast, there has been no attempt by clinicians to define phenotypic subtypes for Bardet–Biedl syndrome. This recessive disorder involves RP, polydactyly, obesity, hypogenitalism, mental retardation and renal anomalies. To date there are four known loci for Bardet–Biedl syndrome, on chromosomes 11q (BBS1),[72] 16q (BBS2),[84] 3p (BBS3)[38] and 15q (BBS4),[81] but as yet no genes have been identified. Finally, the gene defect underlying Refsum disease (RP, peripheral neuropathy, cerebellar ataxia and elevated cerebrospinal fluid protein levels) on chromosome 10p has been identified recently.[65,66] Mutations in phytanoyl-CoA hydroxylase, a peroxisomal protein that catalyses the first step in the alpha-oxidation of phytanic acid, result in accumulation of phytanic acid in blood and tissues.

Central retinal dystrophies

A range of retinal dystrophies can be broadly categorised together on the basis that they affect primarily or solely the central retina. These include cone and cone–rod dystrophy, macular dystrophy, Stargardt's disease, Best's vitelliform macular dystrophy, pattern dystrophy, Sorsby's fundus dystrophy, dominant drusen, central areolar choroidal dystrophy and others. These loci are referenced in Table 1, and are covered in greater detail elsewhere in this issue.

As with RP, the study of these phenotypes is complicated by allelic and locus heterogeneity. Cone and cone–rod dystrophies result from mutations at loci on chromosomes 17p (CORD 5/6),[87,88] 19q (CORD2),[92] Xp (COD1),[12] and Xq(COD2),[22] as well as from mutations in the peripherin/RDS gene on chromosome 6p.[102] Macular dystrophy also results from mutations in the peripherin/RDS gene, while so-called North Carolina macular dystrophy (MCDR1) maps to 6q.[56] Recessive Stargardt's disease has been shown to be due to mutations in the ABCR gene on chromosome 1p, and the same gene has recently been identified as a major susceptibility locus for AMD.[26,27] Dominant Stargardt's loci have been placed on chromosomes 6q[55] and 13q.[78] The TIMP3 gene on 22q is known to be mutated in Sorsby's fundus dystrophy[96] while loci for Best's, cystoid macular dystrophy and for two variants of the phenotype dominant drusen have been mapped to 11q, 7p and 2p respectively.[32,33,58,71] Recently the gene on 3p implicated in the SCA7 phenotype, involving spinocerebellar ataxia and macular dystrophy, has been cloned.[37] Finally it is interesting to note that a locus for atypical vitelliform macular dystrophy on 8q, the first retinal dystrophy linkage ever published, has now been withdrawn.[108]

Other retinal dystrophies

There remain a number of retinal dystrophies that do not fall neatly into the categories described above. In some cases the distinct pathology of these diseases provided a clue to the identity of the gene involved – so-called functional cloning. The first retinal dystrophy for which the genetic basis was elucidated is gyrate atrophy. This chorio-retinal atrophy results from hyperornithinaemia, which in turn is caused by mutations in the ornithine amino-transferase gene on chromosome 10q.[67] Similarly, mutations causing oculo-cutaneous albinism (OCA), a defect of pigmentation in the eye and skin, have been identified in the tyrosinase gene on 11q, an enzyme in the melanin biosynthetic pathway.[76]

Other disease genes in this group, particularly those on the X chromosome, have been identified by analysis of deletion or translocation patients. Another form of ocular albinism (OA1) on chromosome Xp was characterised in this way,[5] though the gene involved in a third form, known as albinism–deafness syndrome (ADFN) on Xq, remains to be found.[21] The genes for choroideraemia and Norrie disease were cloned in a similar fashion, and mutations in the latter were also found to cause X-linked exudative vitreo-retinopathy.[14,15,20] Another locus for familial exudative vitreo-retinopathy has been mapped to chromosome 11q,[73] while a similar phenotype, erosive vitreo-retinopathy, maps to 5q,[46] but the genes involved have not been identified.

The genes for two other forms of retinal dystrophy have been identified recently: one a known gene implicated as a 'positional candidate' and the other a new gene identified by positional cloning. The RetGC gene (also known as GUC2D) on human chromosome 17p encodes a photoreceptor-specific guanylyl cyclase that is thought to function in light adaptation and/or recovery of the dark-adapted state after photoexcitation. Mutations in this gene were shown to cause Leber's congenital amaurosis, the earliest and most severe retinal dystrophy, after linkage analysis in families pinpointed the gene.[89] Researchers have now also identified the gene mutated in retinoschisis, named XLRS1, by mapping ESTs on a physical contig of the Xp22 region.[6]

Finally, several other phenotypes not falling neatly into the central/peripheral disease categories have been mapped to distinct chromosomal regions. Aland Island eye disease, characterised by loss of visual acuity, nystagmus and myopia, maps to Xp11.[19] Achromatopsia (total colour blindness), mapping to chromosome 2cen, also involves symptoms of nystagmus and reduced visual acuity in daylight, as well as photophobia.[34] A locus for autosomal dominant optic atrophy maps to 3p;[42] and the rare helicoid peripapillary chorioretinal degeneration known as atrophia areata maps to 11p15.[68]

Clinical implications and future research

The substantial increase in our understanding of human retinal dystrophies in recent years has taught us much about normal retinal function, but many questions remain. The mechanism by which mutations in so many different genes lead to the common end-point of a degenerating retina is as yet only partially understood. However, hope of widely applicable therapies has come recently from two independent lines of investigation. Firstly, in 1993 Chang and colleagues were able to show that, in three different animal models of RP, the photoreceptors die by the common pathway of apoptosis.[109] There is now increasing evidence that this holds true for a wide range of human retinal dystrophy phenotypes. The apoptotic pathway may therefore be a target for drug or gene therapies, and manipulation of components of it has been shown to reduce the rate of photoreceptor loss in animal models.[110–112]

Secondly, a randomised trial over a 6 year period found that photoreceptor degeneration, as measured by cone electroretinograms, was significantly slowed in RP patients taking vitamin A supplements.[113] Since this trial used an assortment of patients from every inheritance class, the observations may hide a far more significant effect in certain forms of retinal dystrophy. For instance, those RP patients recently found to have mutations in retinoid binding proteins may be particularly amenable to simple dietary treatment. A 1 week course of a high dose of vitamin A (referred to as vitamin A megatherapy) sufficed to abolish night blindness in patients with the early stages of Sorsby's fundus dystrophy.[114] Other therapies that have in the past been tried on similarly heterogeneous patient groups and abandoned may now be found useful in some forms of retinal dystrophy. For instance, when the transgenic rhodopsin-RP mouse is reared in the dark its retina does not degenerate, yet a study of the wearing of dark glasses by human RP sufferers failed to show any significant improvement in prognosis.

Thus while the picture emerging from retinal genetic research is complex, the knowledge it brings may help to tease out clinically relevant details from the existing literature. At the same time genotype/phenotype correlations and knowledge of the frequency of the different retinal diseases will help to direct and improve the service which clinical geneticists can offer to these patients. It is therefore important that the processes of genetic mapping and mutation screening in retinal dystrophy patients and their families continue. This approach will reveal new proteins with important functions in the eye, which will lead to greater understanding of normal eye function and may offer new avenues for therapeutic intervention.

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