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Review

Signal transduction in the retina and inherited retinopathies

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Abstract. In this paper, an attempt is made to highlight some of the recent developments in genetics to understand the group of inherited eye disorders referred to as retinitis pigmentosa (RP). Of the seven genes identified, six are expressed specifically in the photoreceptor cells and four encode the enzymes involved in the phototransduction pathway. A short discussion is presented of the tremendous phenotypic heterogeneity. An understanding of RP requires knowledge of other genetic and environmental factors as well as tests to measure the status of the patient's photoreceptor cells in various disease stages.

Key words. Signal transduction; retina; retinopathies; mutations; rhodopsin; peripherin/RDS; genotype; degeneration.

Introduction

The eye is an interesting system for multidisciplinary studies such as anatomy, biochemistry, physiology, developmental biology and pathology. It is a prominent and easily accessible tissue at very early embryonic development. The precise interactions between and among the diverse parts of the eye provide limitless challenges to address many fundamental biological processes, including neurobiological ones. The retina, a multicellular component of the eye, has provided many challenging opportunities to investigate how the cells generate and maintain their distinctive regional properties while responding and adapting to their varying environmental conditions during the entire life history of an organism. Developments in cell and molecular biology have made it possible to isolate and understand the structure and functions of the proteins involved in phototransduction at the molecular level, and have provided for the first time the tools necessary to determine the genetic basis of several forms of inherited blindness which result from degeneration of the retina. It has now also become possible to investigate the genotype-phenotype relationships in genetic as well as other eye disorders. The purpose of this paper is to highlight some of these advances and to discuss their implications for retinal disorders. Because of space constraints, many original articles are cited by means of reviews. The readers should consult these articles for comprehensive references.

Signal transduction in the retina

It is appropriate to begin with a brief description of the phototransduction process (conversion of photons of light into electrophysiological impulses) which has been extensively studied by many laboratories [1–7]. The photoreceptor cell is made up of two compartments, namely the inner and outer segments. It is in the rod outer segment where the first step in the enzymatic amplification of the light signal takes place. The light is absorbed by the visual pigment rhodopsin which is embedded in the membranes of the photoreceptor outer segment discs. Light-activated rhodopsin then initiates a GTP-GDP exchange reaction with a GTP binding protein called transducin. This reaction releases GTP-alpha transducin (β and γ subunits dissociate from the α subunit). The transducin then activates the enzyme cGMP phosphodiesterase (PDE). Activated PDE rapidly hydrolyses cGMP which is bound to the rod photoreceptor cGMP-gated channel protein. This results in a lowering of the cytoplasmic cGMP concentration and hence closure of the cGMP-dependent cation channel. The closure of the channel causes the hyperpolarization of the rod cell plasma membrane which initiates the visual transduction signal. A decrease in Ca^{++} level stimulates recoverin, which in turn activates guanylate cyclase. This leads to a rise in cGMP production which reopens the cGMP-gated channel. This, together with phosphorylation of photoactivated rhodopsin by rhodopsin kinase, converts the rod cells to the ground state (fig. 1). Similar mechanisms and homologous proteins are found to be involved in phototransduction within cones but the details are different and different genes code for these proteins [8–10].

In several animal models for retinal degeneration, the photoreceptor outer segment, which is the major site of light transduction, has recently been shown to be the site of pathology [11–16]. Homozygote *rds* (retinal degeneration slow) mice are defective in retinal photoreceptors that fail to elaborate outer segments or outer segment discs. The heterozygotes also show an abnormal development followed by degeneration of photoreceptors. In

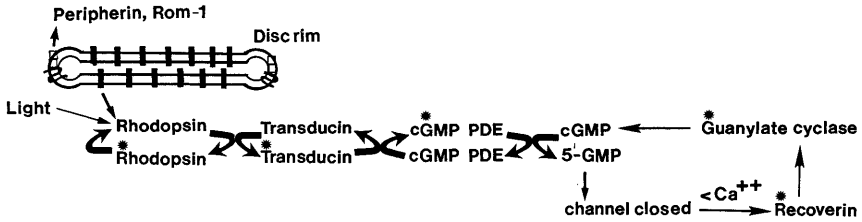

Figure 1. A schematic representation of a rod photoreceptor outer segment. Phototransduction is initiated when rhodopsin localized in the membrane of the photoreceptor outer segment discs is activated by absorbing a photon of light. Activated rhodopsin stimulates transducin, a GTP binding protein. The α-subunit of transducin complexed with GTP dissociates from β, γ transducin and activates cGMP phosphodiesterase (PDE). Hydrolysis of cGMP reduces the cytoplasmic cGMP concentration which causes the closure of the ion-channels in the plasma membrane. The resulting lowered calcium level stimulates recoverin and guanylate cyclase activity and results in a rise in cGMP production that reopens the channels. Peripherin/RDS and ROM1 are localized in the disc rim. The star mark denotes activated molecules.

rd mice the photoreceptor cells were found to degenerate progressively and by 20 days all photoreceptor layers had degenerated. This suggested the possibility that any outer segment protein may be a candidate protein involved in human inherited retinopathies, and has led to extensive investigation by several groups around the world. The following is a brief discussion of these attempts which focus on the most common cause of retinal degeneration in human, namely retinitis pigmentosa.

Retinitis pigmentosa (RP)

The term retinitis pigmentosa (RP) is used to describe a large heterogeneous group of progressive hereditary degenerative diseases of the retina, affecting the photoreceptors of the eye [17–25]. It is the most common degenerative disorder and is untreatable. An estimated 1.5 million people are affected by RP around the world and one in 3,000 in the United States. The most common symptoms include night blindness, progressive concentric reduction of the visual field, abnormal retinal electrophysiology and an abnormal accumulation of pigmentation in the retina. The clinical manifestations are variable between and within the affected family [26]. The condition can be inherited as an autosomal dominant (19%), autosomal recessive (19%), or X-linked recessive (8%) condition, on a sporadic (simplex) basis (46%) and for undetermined reasons (8%). To date, autosomal dominant (*adRP*) loci have been mapped on chromosome 1[27], 3q (rhodopsin), 6p (peripherin/RDS), 7p, 7q, 8q, 17p, 17q and 19q [25, 28–33], autosomal recessive (*arRP*) loci on 1q, 3q, 4p14, 4p16, 5q and 6p [25, 34–36] and three X-linked (*X1RP*) loci have been proposed on the short arm of the X-chromosome [37–39]. In typical cases of RP, rod photoreceptors are more severely affected early in the disease. Later in the disease cone photoreceptors degenerate as well. However, both allelic and nonallelic heterogeneity and marked variability in expressivity of the retinitis pigmentosa phenotype was also found in autosomal disease [40].

Rhodopsin

Rhodopsin, the light receptor molecule is a photopigment protein expressed specifically in rod photoreceptors [41, 42]. It is an abundant protein of the disc membranes of the outer segment and is responsible for mediating vision at low light levels. It contains 348 amino acids and is folded into three structural domains. The protein is bound to 11 *cis*-retinal and upon photoactivation undergoes conformational change and activates transducin. It is composed of seven helical transmembrane domains bounded by cytoplasmic and intradiscal loops. The intradiscal domain plays a critical role in forming a properly folded structure.

Rhodopsin gene mutation

Since the first report by Dryja and associates [43] a variety of rhodopsin mutations (table 1) has been described [24, 44–48]. Many of these are missense mutations and are found only in single families. Approximately 20% of adRP are now believed to be caused by mutations in the rhodopsin gene. Despite overwhelming evidence that mutations in the rhodopsin gene can cause RP, the mechanisms by which defective rhodopsin leads to RP or cell death is not understood. The pattern of distribution of mutations in rhodopsin also does not seem to provide any clue regarding the importance of any protein domain to produce the clinical features of RP, although mutations in the transmembrane domain and around the disulphide bonds produce more severe disease compared to the changes in the carboxy terminal domain. Many mutations would be expected to produce structural abnormality in opsin, such as folding errors. Transfection experiments in human embryonic kidney cell lines [49–51] and COS-1 cells [52] revealed three functional classes of mutations, but failed to show a common abnormal property shared by them all. Some of the mutant opsins bind the chromophore at a wild-type level and are transported to the cell surface but others do not bind the chromophore (class I). Some mutant proteins fail to accumulate in the cell membrane (class II), while others behave like normal proteins.

Some fail to activate transducin and remain in the endoplasmic reticulum (class III), and others constitutively activate transducin [53, 54]. Some mutant opsin molecules appear to be misrouted and are found to be present not only in the outer segment but also in the synaptic layer [55]. This may interfere with synaptic transmission. The removal of carboxy-terminal amino acids inactivates rhodopsin [56].

Although many mutant proteins show folding defects, abnormal sensitivity to light and less efficient activation of transducin, it is not clear why patients within and between families with the same gene defect show differing degrees of severity of the disease. This variable clinical expression among patients of a comparable age with the same gene defect appears to be common for many rhodopsin gene mutations. For instance, a conservative change at codon 137 (Val-137-Met) seems to produce only mild symptoms in some affected individuals [57] and mutation at codon 136 (Y136X) produces no apparent visual problems in younger individuals [58]. Patients carrying a Pro-347-Arg mutation show less severe disease and below the age of 40 do not develop retinal hyperpigmentation [59] whereas patients with a Pro-347-Leu mutation display a significantly smaller visual field area, more extensive impairment and a range of abnormality among different patients [60]. If these mutations change the shape of the C-terminal end and affect the light-dependent phosphorylation and activation of transducin [61, 62], it is not clear how these alterations are associated with variable phenotypes. Mutation at codon 346 [Ala-346-Pro] likewise produces night blindness in early childhood [63], while alteration at codon 345 (Val-345-Leu) produced a mild phenotype [64] and at 344 (Gln344X) young patients are asymptomatic [65]. The mutant Q344ter, on the other hand, is indistinguishable from wild-type rhodopsin in its ability to activate transducin. Three young women in a family carrying this mutation did not have a history of night blindness and visual field loss and appeared normal upon eye examination [65]. However, immunological localization and transgenic mice experiments revealed a defect in localization to the photoreceptor outer segment [51, 66]. Although the deletion of codon 341–343 of rhodopsin substantially altered the C-terminus of the proteins, patients carrying this mutation produced a relatively mild phenotype and night blindness did not occur before the age of 16 [67]. Patients with a Pro-23-His mutation are known have more severe disease and substantial heterogeneity with respect to age of onset [68–71]. In the early stages of the disease cone sensitivity is normal but rod sensitivity is mildly abnormal throughout the retina. In more severely affected patients some retinal regions show mild rod loss and other regions have severe rod and cone dysfunction. One family member carrying a Cys-187-Tyr mutation was significantly less affected than his younger relative [72]. This mutation has changed the residue necessary for the formation of a highly conserved disulphide bond and causes an early onset of dominant retinitis pigmentosa. Most of the mutations in the intradiscal domain (codon 17, 23, 106, 182 and 190) or within the membrane of the disc (codon 58 and 267) are associated with a mild phenotype and show changes within the inferior and inferonasal parts of the retina. They usually show a better visual prognosis [73–78] such as a larger visual field and better dark adapted sensitivity. However, in some cases patients had more extensive functional impairment and more regional retinal pigment changes (Pro-23-His and Asp-190-Tyr). A quantitive change in the abnormal rod dark adaptation has been reported for Thr-58-Arg, Thr-17-Met, and Pro-23-His. Two families carrying Arg-135-Leu and Arg-135-Try, had neither detectable rod function nor measurable rhodopsin. Thus, there is a difference in patterns of rod function in patients with different rhodopsin mutations. How different amino acid substitutions can result in a phenotypically different degree of severity remains to be understood. A variable phenotype has also been observed in two mutations (Leu-40-Arg and Thr-58-Arg) affecting the first transmembrane domain of rhodopsin [79]. The insertion mutation disrupting the 5′-splice junction of exon 5 causes a later onset of retinal dysfunction and is associated with a more variable phenotype than a Leu-40-Arg mutation. A deletion mutation

Table 1. Rhodopsin gene mutation in retinitis pigmentosa and related disorders[a].

Mutation	Class[b,c]	Mutation	Class[b,c]	Mutation	Class[b,c]
T4K	III[b]	R135L	II[c]	E249X	
N15S		R135P		P267L	
T17S		C140S		A292E	
T17M	III[b], II[c]	A164E		K296E	II[b]
P23H	III[b], II[c]	C167R	II[b]	K296M	
P23L		P171L	II[b]	L328P	
Q28H	III[b]	P171S		E341K	
L40R		Y178C	II[b], II[c]	T342M	
F45L	I[b], I[c]	P180A		Q344X	I[b], I[c]
L46R		E181K	II[b]	V345L	
G51A		G182S		V345M	I[b]
G51V	III[b]	S186P	II[b]	P347R	
G51R	III[b]	C187Y		P347A	
P53R	III[b]	G188R	II[b]	P347S	I[b]
T58R	I[b], II[c]	G188E		P347Q	
Q64X		D190N	I[b]	P347L	I[b], I[c]
V87D	III[b], II[c]	D190Y	II[b]	P347T	
G89D	III[b], II[c]	D190G	I[b], II[c]	del. 68–71	III[b]
G90D	III[b]	M207R		del. 255	
G106R	III[b]	V209M		del. 264	
G106W	III[b], II[c]	H211R		del. 340 (lbp)	
C110Y	III[b]	H211P	II[b]	del. 341–343	
G114D		M216K		del. 340–348	I[c]
L125R	I[b]	F220C		4th intron donor/splice	
R135G	I[b]	C221R		junction	
R135W	II[c]	C222R	II[b]	4th intron insertion	

[a]See refs. 24, 44, and 45 for original articles.
[b]COS cell transfection assay [52].
[c]Embryonic kidney cell assay [49–51].

in exon 5 [80] at the 3′-end [81] and mutation in the 3′-acceptor splice site of intron 4 [82] of the rhodopsin gene have also been shown to be responsible for dominant diseases.

Mutation in the rhodopsin gene has also been reported to be the cause for autosomal recessive [83] and simplex cases of retinitis pigmentosa [84, 85] and congenital stationary night blindness [86, 87]. The latter (CSNB) is of particular interest. Although CSNB involves night blindness similar to retinitis pigmentosa, it does not show further retinal degeneration. In vitro studies on the two mutations (Gly-90-Asp and Ala-292-Glu) have suggested a continuous activation of transducin by the mutant opsin, and this is believed to be equal to constant exposure to environmental light [88–91], causing photoreceptor degeneration in vivo. Although the molecular basis of the rod system abnormality in any form of CSNB has not been demonstrated and a number of rhodopsin mutations [53, 92, 93] consistently activate transducin in an in vitro assay system [53], experiments using transgenic mice with these mutant genes [94, 95] do not support the equivalent light hypothesis as a mechanism for photoreceptor degeneration in CSNB. In support of this finding is the fact that patients with CSNB show preserved functioning of the rods despite extensive and life-long night blindness. They also retain daytime vision throughout life and there is no degeneration of rod or cone photoreceptors during the life of the patient. Rhodopsin densitometry assay in vivo also supports this result. However, in some cases of retinitis pigmentosa, the equivalent light theory may explain [96, 97] the degenerative changes although it is again not the case for the transgenic mice carrying the mutation Lys-296-Glu [98].

Table 2. Phosphodiesterase and cGMP-gated channel gene mutation.

Phosphodiesterase			cGMP-gated channel	
Subunit	mutation	reference	mutation	reference
α	S354R	100	E76X	109
	W561X		L139X	
	Y583X		S316F	
			R654 (1bp del.)	
β	A155S	102		
	E166K	102		
	Y219H	102		
	Q298X	102, 104		
	P496 (1bp del)	102, 104		
	L527P	102, 104		
	R531X	102, 104		
	Y557H	102, 104		
	G576D	101		
	R602H	102		
	H620 (1bp del)	101		
	K706X	102, 104		
Intron 2 splice/acceptor site		101		
Intron 8 splice/donor site		102, 104		
71 bp tandem duplication in exon 1		103		

X = stop codon.

Rod transducin gene mutation

Rod transducin is a second component of the phototransduction cascade and is a trimeric protein consisting of α, β, and γ subunits. After the absorption of light, the active rhodopsin binds to hundreds of copies of transducin. This induces the separation of β and γ subunits from the GTP-bound α subunit. This is the first chemical signal that starts the amplification of the signal in the visual process. A missense mutation (Gly-38-Asp) in the α subunit of rod transducin has been identified [99] in one form of congenital stationary night blindness. A constitutively active mutant transducin is believed to be the cause of rod photoreceptor dysfunction. Further studies are needed to understand better the structure/function relationship as well as the active and inactive stages of rod transducin.

Mutation in the cGMP phosphodiesterase gene (cGMP PDE)

In several animal studies it has been shown that defects in cyclic mucleotide metabolism are associated with retinal degeneration and these abnormalities are the result of deficient cGMP-phosphodiesterase. Rod specific cGMP phosphodiesterase (PDE) is the third key enzyme in the signal transduction and consists of two large catalytic (α and β) and two small, identical inhibitory (γ) subunits. The activated α-subunit of transducin carrying GTP removes the inhibitory subunits, thereby activating the PDE. The activated PDE in turn hydrolyses many molecules of cGMP and causes the channel to close. This leads to hyperpolarization of the plasma membrane. Although the PDE gene is not the main gene responsible for RP, it accounts for 4–5% of cases. In some recessive pedigrees, several nonsense and missense mutations in the α and β (but not γ) subunits of the gene have been identified (table 2) as the cause of RP [100–104]. In many cases the mutant proteins are non-functional (truncated proteins) and presumably lead to the accumulation of cGMP [105] in the outer segment resulting in a large increase in the opening of the cGMP-grated channel which increases the intracellular Ca^{++}.

Mutation in the cGMP-grated channel

The cGMP-grated cation channel is the final component of the phototransduction cascade and is located on the plasma membrane of the rod outer segment. Its open and closed configuration depends on the cytoplasmic concentration of cGMP. It is composed of α and β

subunits [106] and another γ subunit of unknown function [107]. It is not only sensitive to cGMP but also regulated by calmodulin [108]. In some recessive families, mutations (table 2) in the gene encoding the α subunit of the cation channel have been described [109]. The mutant proteins when expressed in vitro are found to be predominantly present inside the cell and are not targeted to the plasma membrane. Since the channel is a very minor protein and is exclusively localized in the plasma membrane, folding error, aberrant disc structure and Ca^{++}-triggered cell death are unlikely. An equivalent light hypothesis [91] has been proposed as a mechanism for rod cell death in these patients.

Mutation in the peripherin/RDS gene

RP is also caused by mutation in the other genes which are not involved in the phototransduction pathway. The peripherin/RDS which does not absorb light is localized in the rim region of the outer segment disc, and its function is to maintain the structure of the disc membrane [110, 111]. It is a glycoprotein of 39 kDa (346 amino acids), is highly conserved among mice, cattle, rats and humans and is thought to play an important role in the assembly, orientation and physical stability of the membranous disc of rods and cones.

Mutations in the human peripherin/RDS gene have been found (table 3) in families with RP [44, 112–120], butterfly shaped pigment dystrophy [121–123], retinitis punctata albescens [124], pattern dystrophy [125], macular dystrophy [126–128], fundus flavimaculatus [129], bull's eye maculopathy [130], central areolar choroidal dystrophy [131], and cone-rod dystrophy [132, 133]. Thus, mutations in the peripherin/RDS gene are associated with radically different phenotypes. Different mutations or the same mutation in the peripherin/RDS gene in the same family give rise to different retinal dystrophies which differ markedly from each other. A three base pair (bp) delection of codon 153 or 154 can produce clinically disparate phenotypes even within the same family [129]. Patients with Gly-167-Asp and Asn-224-Lys mutations have widely different clinical phenotypes [121, 130, 132]. In some families, there is a selective loss of central vision whereas loss of peripheral vision occurs in others. Many mutations which have been implicated in RP have been found either in the second and third transmembrane domain or in the second intradiscal loop of the protein. Amino acid substitution at the carboxyl end of the protein may not have any effect on photoreceptor function [134]. In some cases, the altered protein may result in either a deficiency of product or it may influence other proteins. A reduction in the amount of protein may be deleterious to the photoreceptor. How this alteration in the peripherin/RDS gene results in photoreceptor degeneration remains obscure. It is also difficult to establish a close relationship between phenotype and genotype. Since mutations in the same gene can produce such radically different phenotypes, other gene products or environmental factors could be associated with these diseases.

Table 3. Mutation in the peripherin/RDS gene.

Mutation	Phenotype	Reference
del 25	retinitis punctata albescens	124
R46X	RP	112, 113
del 118/119	RP	126
L126R	RP	44
Ins 140	pattern dystrophy	125
R142W	central areolar choroidal dystrophy	131
L153R	RP	132
del 153/154	RP, pattern dystrophy, fundus flavimaculatus	129
G167D	butterfly pigment dystrophy	121
R172W	macular dystrophy	126, 127
R172Q	macular dystrophy	126, 127
Y184S	cone-rod dystrophy	132, 133
L185P	RP	117, 119
P210R	macular dystrophy	132
S212G	RP	115
C214S	RP, rod-cone dystrophy	118, 132
P216S	RP, rod-cone dystrophy	116, 132
P216L	RP	119
del 219	RP, rod-cone dystrophy	119, 132
N224K	RP, bull's eye maculopathy	120, 130
N224H	cone-rod dystrophy	132
N244K	rod-cone dystrophy	132
N244H	cone-rod dystrophy	132
Y258X	vitelliform macular dystrophy	126
G266D	RP	44
del 307	RP	44
del exon-2 and 3	butterfly pigment dystrophy	44

Mutation in the rod outer segment membrane 1 (ROM 1) gene

The ROM1 is an integral membrane protein and is very similar to peripherin/RDS [135]. It is expressed specifically in the retina, localized to the disc region of the rod outer segment and mapped to chromosome 11q [136, 137]. It interacts with peripherin/RDS to form homodimers [137]. Although the exact function of ROM1 is not known, mutations have been reported in three families with RP. The same three families also show mutations in the peripherin/RDS gene and hence the inheritance was termed digenic [117]. How this null mutation in the gene results in photoreceptor degeneration remains to be established.

Genotype-phenotype correlation

One of the major challenges in human genetics is to establish the genetic and phenotypic relationships which contribute to the development of hereditary disorders. In general, for most genetic disorders, it is thought that a variety of different mutations in a single gene can be responsible for one particular phenotype. However, a

growing body of recent evidence suggests that the different or the same mutations within a single gene can give rise to highly distinct phenotypes. For instance, mutations in the peripherin/RDS gene, which is expressed in both cones and rods of the retina, appear to give rise to retinitis pigmentosa, retinitis punctata albescens, butterfly dystrophy and macular dystrophy. The phenotypic expression of the disorder also varies in the same family having an identical mutation, suggesting that photoreceptor cells respond differently to different mutations, or even to the same mutation. Adrenolukodystrophy (ALD) is an X-linked disorder and exhibits a wide variety of clinical phenotypes [138, 139] within individuals in a single family carrying the mutant allele. In the case of optic neuropathy, monozygous twin brothers carrying the same mutation in the mitochondrial DNA were found to be discordant for the disorder [140]. In addition, identical mutations in the fibroblast growth factor receptor 2 appears to cause two different disorders: Pfeiffer and Crouzon Syndrome [141]. Similarly, different mutations in the *COLA1A1*, *COL1A2*, *COL2A1*, *PAX3* and androgen receptor genes produce a variety of phenotypes [142–145].

Monogenic diseases such as Duchenne muscular dystrophy and cystic fibrosis are relatively rare conditions and usually follow a Mendelian inheritance pattern. On the other hand, many complex diseases such as diabetes do not strictly follow Mendelian genetics, but are often associated with one or several genes [146–148] in a family and environment. This phenomenon of clustering and environmental influence is often referred to in the literature as 'nature versus nurture'. Studies on identical and dizygotic twins in some cases may provide information regarding the genetic contribution to the phenotype, but an estimation of the individual gene contribution to the phenotype is often difficult to make in humans. On the other hand, identification of clustered genes or modifier loci may provide opportunities to address the question of 'nature versus nurture' in the future.

While most, if not all, of the above mutations occur by substitution, it is not clear why and how a single gene defect produces such clinically distinct types and sometimes tissue-specific disorders. Does this mean that a single gene product has multiple functions? An allelic heterogeneity [149–151] is considered to be the most probable explanation for phenotypic variability. In addition genetic mosaism (heteroplasmic), in the case of mitochondrial disorders may explain subtle and not so subtle phenotype differences in individuals with the same mutation. It is conceivable that different mutations will affect (i) protein-protein interaction, (ii) dimerization, (iii) gain or loss of function (because of mutation of gene promoters or other non-translated regulatory elements), (iv) specific interactions with the modifier loci, and (v) regulation of neighbouring genes. Additionally, the difference and severity in phenotypic expression can be explained by the effect of an additional causative or a common polymorphic mutation in the same gene, as was shown recently for the prion [152] and Gaucher [153] disorders. The difference in phenotype could also be due to the differential function of a protein. This differential function of a particular gene product (or a mutant protein) is determined by a secondary interaction with one or more of the other gene products in our total genetic make-up and with environmental factors. This is usually referred to in the literature as penetrance or variable expressivity. Since transgenic mice of different strains harbouring a modified gene often display significant differences in phenotypic expression [154, 155] of a trait, it appears very likely that an individual's genetic background may play a role in the clinical expression of genetic disorders.

Is there a relationship between genotype and phenotype and if so, how much does a gene alteration contribute to it? This subject has been recently reviewed [156] and will not be discussed further. Since disease phenotypes can also result from causes other than a gene mutation [156], it is certain that non-genetic factors also play a major role in determining the phenotype [157, 158] and that genes are necessary but not sufficient to produce variable phenotypes. In that respect, it is clear that even monogenic disorders are multifactorial and hence subject to variation in their expression. It is also possible that there is a considerable observer variation in the clinical diagnosis of certain diseases (e.g. Crouzon Pfeiffer etc.), which can lead to confusion relating to the molecular pathology. In additon, we now know that only a fraction of our genome is transcribed and an even smaller fraction is processed into mRNA to be translated into protein. Furthermore, this process varies considerably between cells and individuals. Phenotypic variations may not be surprising and are most likely the direct result of variations in the number of informational molecules in a given cell. Hence, it is difficult to imagine a direct relationship between genotype and phenotype. Phenotypes are the ultimate consequence of a multi-stage processing of multifactorial interactions and it is difficult to understand how this is dictated by our genome. Mutation analysis alone is not sufficient to understand the disease phenotype. The structure or function of a single gene product, its interaction (epigenetic) with other genes, interaction with metabolites and the influence of the external environment are all likely to be involved in determining the phenotype.

In summary, phenotypes are the final result of the interactions of genetic and non-genetic factors, including the environment. If phenotypes are encoded in the genome then it is possible to predict each phenotype because predetermined genetic alterations can be analysed and such phenotypes are non-variable. How-

ever the observations cited above strongly support the belief that strict rules encoded in the genome cannot explain the wide variability seen in the phenotype. The phenotypes are not entirely dependent on either the information in the genome or environmental factors alone, but depend upon the ultimate result of prolonged interaction between genes, their products, metabolites, ions and environmental factors and hence are bound to vary considerably from individual to individual. These interactions between internal and external factors cannot be separated from one another, but are an integral part of the organism.

Concluding remarks

A new era began in 1990 with the hope that identification of gene mutations would shed some light on heritable photoreceptor disorders and that this would lead to a new treatment strategy for a cure. To date, six genes have been identified in photoreceptor disorders and four of them have been found to encode enzymes of the phototransduction cascade which are specifically expressed in photoreceptor cells. Of these, rhodopsin has received greater attention because of its natural abundance in the cell and its primary role in phototransduction. Close to 70 mutations have been described to be linked to some form of RP and the majority have been shown to produce a folding error which may lead to impairment of the protein delivery system of the cell. There appears to be no simple correlation between genotype and phenotype. The biochemical mechanisms underlying retinal degeneration still remain to be understood. The production of an aberrant disc structure due to mutations in the peripherin/RDS gene could produce cellular damage or interfere with folding or transport of the other proteins, but we are still ignorant of the biochemical basis of several different clinical phenotypes (e.g. adRP arRP CSNB and macular degeneration) and of the slow deterioration of rods and cones. The proposed pathogenic hypothesis known as the 'constant equivalent light model' failed to explain (at least in two cases) the cell death which is caused by overstimulating the phototransduction pathway. Therefore, cell death must be triggered by mechanisms other than over-stimulation, which is consistent with the fact that RP is also caused by mutations in the gene other than phototransduction defects.

Although the clinical manifestations of RP often appear to be similar in different RP patients, it is a disease of several different genes. A compilation of the mutations [29, 44, 45, 159] occurring in different genes animal models [160] and the experiments described using cultured cells [50, 93] are not enough to answer the questions: (i) why cone cells are drastically affected by mutations in the rod protein, (ii) why different mutations in different photoreceptor genes all seem to lead to cell death, (iii) what actually triggers the cell death, (iv) how the mutation causes the disease, (v) why only a part of the retina degenerates while the remainder of the retina in the same eye appears normal, (vi) why patients having the same mutation show different symptoms and (vii) why some mutations show early onset while others show late onset of the disease. Transgenic and tissue culture experiments using mutant genes have given ambiguous results. Possible explanations for the failure of the animal model and the tissue culture system are that animal models cannot yield exactly the same human condition and that tissue culture cells do not develop outer segment. The results discussed in the previous sections may also indicate that mutation by itself is necessary but not sufficient. It is likely that other factors, such as genetic and environmental ones, are needed to produce degeneration. On the clinical side, however, a more precise understanding of the molecular mechanisms in a patient's rods is needed to develop an effective therapy.

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