Genome Medicine

REVIEW

Retinitis pigmentosa and allied conditions today: a paradigm of translational research

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Abstract

Monogenic human retinal dystrophies are a group of disorders characterized by progressive loss of photoreceptor cells leading to visual handicap. Retinitis pigmentosa is a type of retinal dystrophy where degeneration of rod photoreceptors occurs at the early stages. At present, there are no available effective therapies to maintain or improve vision in patients affected with retinitis pigmentosa, but post-genomic studies are allowing the development of potential therapeutic approaches. This review summarizes current knowledge on genes that have been identified to be responsible for retinitis pigmentosa, the involvement of these genes in the different forms of the disorder, the role of the proteins encoded by these genes in retinal function, the utility of genotyping, and current efforts to develop novel therapies.

Introduction

Human retinal dystrophies (RD) are a group of disorders characterized by a primary and progressive loss of photoreceptor cells leading to visual handicap. Monogenic RD are rare diseases. The most common form of the disease, retinitis pigmentosa (RP), is characterized by primary degeneration of rod photoreceptors and has an estimated prevalence of around 1 in 4,000 [1-4], although higher frequencies have been reported in some Asian populations (1 in 930 in South India [5], and approximately 1 in 1,000 in China [6]). RP constitutes 85 to 90% of RD cases.

The first symptoms of RP are retinal pigment on fundus examination, and night blindness, followed by progressive loss in the peripheral visual field, eventually leading to legal blindness after several decades. The clinical aspects of RP are shown in Table 1. The clinical presentation can be macular, cone or cone-rod dystrophy (CORD), in which the decrease in visual acuity predominates over the visual field loss, or it can be the only symptom. Cone dystrophy is an inherited ocular disorder characterized by the loss of cone cells, which are the photoreceptors responsible for central and color vision. Typically, age of onset is early teens, but it can be very variable, ranging from congenital forms of the disease (Leber's congenital amaurosis (LCA)) to late-onset RD.

RP is usually non-syndromic (70 to 80%), but there are also more than 30 syndromic forms, involving multiple organs and pleiotropic effects, the most frequent being Usher syndrome (USH; approximately 15 to 20% of all RP cases). USH associates RP with sensorineural deafness and sometimes vestibular dysfunction. The second most common syndromic form is Bardet-Biedl syndrome (BBS), which accounts for 20 to 25% of syndromic forms of RP or approximately 5% of cases of RP. Patients with BBS typically present with RP, obesity, polydactyly, renal abnormalities and mild mental retardation.

It is worth noting that USH and BBS are genetically as heterogeneous as isolated RP. To date, nine genes have been identified for USH and 14 for BBS. The existence of patients lacking mutations in any of the identified genes indicates that at least one more gene remains unidentified for both syndromes.

Other syndromic forms of RP include associations with hearing loss and obesity (Alström syndrome), dysmorphic face and kidney deficiency (Senior-Locken syndrome), and metabolic disorders [7]. Table 2 shows the most common disorders involving non-syndromic and syndromic RP.

Patterns of inheritance in retinitis pigmentosa

Both RD and RP show great clinical and genetic heterogeneity, and they can be inherited as autosomal-recessive (ar), autosomal-dominant (ad) or X-linked (xl) traits. Other atypical inheritance patterns, such as mitochondrial, digenic, triallelic and isodysomy, have also been associated with some RP cases [8].

Almost half of RP cases are sporadic, without any history of RD in the family. Diverse patterns of

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Table 1.Clinical signs of retinitis pigmentosa and cone-rod dystrophy

Clinical signs	
Visual function	Impaired night vision (nyctalopia), myopia (frequently), progressive loss of visual acuity
Visual field	Loss of peripheral vision in early stages, progressive loss of central vision in later stages, ring scotoma, tunnel vision
Eye fundus	Bone spicule deposits in peripheral retina, attenuation of retinal vessels, waxy pallor of the optic disc
Eye movement	Nistagmus
Electroretinogram	Diminution or abolishment of the a-waves and b-waves

Table 2. Non-syndromic and syndromic retinal dystrophies and inheritance pattern

Retinal dystrophy	Inheritance
Non-syndromic	
Retinitis pigmentosa	ad, ar, xl, digenic
Cone or cone-rod dystrophy	ad, ar, xl
Leber congenital amaurosis	Mainly ar, rarely ad
Stargardt disease	Mainly ar, rarely ad
Fundus flavimaculatus	ar
Congenital stationary night blindness	ad, ar, xl
North Carolina macular dystrophy	ad
Sorsby's macular dystrophy	ad
Pattern macular dystrophy	ad
Vitelliform macular dystrophy (Best's disease)	ad (incomplete penetrance)
Choroideremia	xl
X-linked retinoschisis	xl
Gyrate atrophy	ar
Syndromic	
Usher syndrome	ar
Bardet-Biedl syndrome	ar, oligogenic
Senior-Locken syndrome	ar
Alport syndrome	xl
Älmstron syndrome	ar
Joubert Syndrome	ar
Nephronophthisis	ar, oligogenic
Cockayne syndrome	ar
Refsum disease	ar
Autosomal dominant cerebellar ataxia type 7	ad
Norrie disease	xl

ad: autosomal dominant; ar: autosomal recessive; xl: X-linked.

inheritance have been reported for non-syndromic cases of RP and their families depending on the geographical origin, the sample size of the study and the methods for clinical ascertainment. A reliable estimate for the percentages of each inheritance pattern could be 15 to 25% for autosomal-dominant RP (adRP), 35 to 50% for autosomal-recessive RP (arRP), 7 to 15% for X-linked RP (xlRP), and 25 to 60% for syndromic RP [9] (Table 3).

However, well-known genetic phenomena that alter Mendelian inheritance have also been observed in RP. Incomplete penetrance [10] and variable expressivity have been reported in many families with RP. The literature offers many examples of variable degrees of severity of RP among members of the same family carrying the same mutation [11]. In xlRP forms, female carriers sometimes present RP symptoms and can be as affected as male carriers. One explanation for this might be lyonization, that is, the random inactivation of one X chromosome in females to compensate for the double X gene dose during early developmental stages. The inactivation of the X chromosome not carrying the mutation in a cell or cell population that will later develop into the retina could lead to an active mutated RP gene in the female carrier.

Genes involved in retinitis pigmentosa

The overwhelming pool of genetic data that has become available since the identification of the first mutation associated with RP in humans (a proline to histidine change at amino acid position 23 in rhodopsin, reported by Dryja *et al.* in 1990 [12]) has revealed the genetics of RD to be extremely complex. Research into the molecular causes of RD has revealed the underlying disease genes for about 50% of cases, with more than 200 genetic loci described [13]. These genes are responsible not only for RP, but also for many other different clinical entities such as LCA, macular degeneration and CORD. To date, 26 genes have been identified for arRP and 20 for adRP, and two genes on the X chromosome (xlRP). For a number of these genes, some mutations in the same gene lead to autosomal-dominant forms, while some other mutations lead to autosomal-recessive forms.

Different mutations in several genes lead to syndromic forms such as USH or isolated RP (*USH2A* gene) or non-syndromic deafness (*MYO7A*, *CH23*, *PCDH15*, *USH1C* and *USH1G*), and mutations in the same gene can cause different clinical entities, as has been observed for *ABCA4*, which is implicated in arRP, autosomal-recessive macular dystrophies (arMD) and autosomal-recessive CORD (arCORD). Furthermore, most of the mutations causing RP are exclusive to one or a few individuals or families. Common mutations and hot spots are rare; therefore, there is a need for large and time-consuming mutation screenings to achieve a molecular diagnosis of RP in patients. In addition, there is no clear genotype-phenotype correlation and, in many cases, relatives

Table 3. Geographical distribution of genetic types

Country and reference	Non-syndromic RP (*n*)	adRP (%)	arRP (%)	xlRP (%)	Syndromic RP (%)
Spain [55]	1,717	15	34	7	41 (3 unclassified)
France [56]	153	19	35	4.1	41.3
The Netherlands [57]	575	22.4	30.1	10.4	37.1
Switzerland [1]	153	9	90	1	-
Germany [58]	250	25.2	16.4	10	48.4
UK [59]	300	39	15	25	21
USA [60]	138	22	10	14	37
USA [61]	489	14.1	13.7	7	65.2
Japan [62]	1,091	2.1	40.1		43.2
Japan [63]	434	16.9	25.2	1.6	56.3
China [64]	150	13.3	67.3	2.7	16.7
South Africa [65]	63	21	15	10	54
USA [66]	68	6	13	7	74

adRP: autosomal-dominant retinitis pigmentosa; arRP: autosomal-recessive retinitis pigmentosa; RP: retinitis pigmentosa; xlRP: X-linked retinitis pigmentosa.

bearing the same mutation display very different forms of RP in terms of age of onset and severity.

Many genes and proteins are associated with RD. These proteins are involved in retinal functions, but they can also play other roles such as degradation of proteins in the retinal pigment epithelium, and ionic interchange or trafficking of molecules in the ribbon synapse of photoreceptors. Tables 4, 5, 6 and 7 summarize the genes involved in RD, their chromosomal locations and functions, and the proteins they encode. The major pathways involved in pathogenesis of RP are discussed below.

Phototransduction

Phototransduction is the process through which photons are converted into electrical signals. It begins with the light-induced isomerization of the ligand of rhodopsin, which is 11-cis retinal, and the activation of rhodopsin. Rhodopsin undergoes a change in conformation upon photoexcitation and activates the G protein transducin. GDP-bound inactive transducin exchanges GDP for GTP, and GTP-bound active transducin increases the activity of cGMP phosphodiesterase. The result is decreased levels of cGMP in the cytoplasm, and this causes the closing of cGMP-gated ion channels and leads to membrane hyperpolarization. The recovery of the phototransduction process is carried out by the phosphorylation of rhodopsin by a receptor-specific kinase, rhodopsin kinase. The phosphorylated photoactivated rhodopsin is bound by arrestin, thereby terminating activity of the receptor in the signal transduction process. Mutations in the gene encoding rhodopsin (*RHO*) are responsible for adRP, arRP and dominant congenital stationary night blindness. Mutations in the genes for cGMP phosphodiesterase alpha and beta subunits (*PDE6A* and *PDE6B*, respectively) are responsible for arRP and dominant congenital stationary night blindness. Mutations in the genes encoding the rod cGMP-gated channel alpha and beta subunits (*GUCA1A* and *GUCA1B*, respectively) are responsible for arRP, while arrestin (*SAG*) is involved in Oguchi disease. The genes encoding guanylate cyclase activating protein 1B (*GUCA1B*) and cone alpha subunit of cGMP phosphodiesterase (*PDE6C*) are responsible for dominant MD and arCORD, respectively.

Visual cycle

After isomerization and release from the opsin protein, all-trans retinal is reduced to all-trans retinol, and it travels back to the retinal pigment epithelium to be 'recharged'. It is first esterified by lecithin retinol acyltransferase and then converted to 11-cis retinol by RPE65. Finally, it is oxidized to 11-cis retinal before traveling back to the rod outer segment, where it can again be conjugated to an opsin to form a new functional rhodopsin. Many proteins involved in the chemical transformation and transport for retinoids are causative agents of RD. Mutations in the gene that encodes the retinal pigment epithelium-specific 65kDa protein (*RPE65*) can cause arRP or autosomal-recessive LCA (arLCA); *ABCA* encodes a retinal ATP-binding cassette transporter, and mutations lead to a wide variety of clinical symptoms, including arRP, autosomal-recessive Stargardt disease and arCORD; the gene *IRBP1* encodes the interphotoreceptor retinoid binding protein and mutations cause arRP; *LRAT* encodes lecithin retinol acyltransferase and mutations cause arRP and arLCA. Mutations in up to 13 different genes involved in the visual cycle lead to different retinal degenerations, highlighting the importance of this biochemical pathway in the physiology of vision.

Table 4. Pathways related to retinal dystrophies

Pathway	Genes causing retinal dystrophy	Phenotypes
Phototransduction	*CNGA1*, *CNGB1*, *GUCA1B*, *RHO*, *PDE6A*, *PDE6B*, *PDE6C*, *SAG*, *CNGB3*	adRP, arRP, adMD, dCSNB, Oguchi disease, arCORD
Visual cycle	*ABCA4*, *RGR*, *RLBP1*, *BEST1*, *IRBP*, *RPE65*, *CA4*, *RDH12*, *IDH3B*, *ELOVL4*, *PITPNM3*, *GUCY2D*	adRP, arRP, arMD, adMD, arCORD, adCORD, coroid sclerosis, arLCA
Phagocytosis of rod outer segments	*MERTK*	arRP
Retinal development	*CRX*, *NRL*, *NR2E3*, *SEMA4A*, *RAX2*, *PROM1*, *TSPAN12*, *TULP1*, *OTX2*	adRP, arRP, adLCA, arLCA, adCORD, adMD, FEVR
Ciliary structure	*CEP290*, *RP1*, *USH2A*, *CRB1*, *RP2*, *RPGR*, *RPGRIP1*, *LCA5*, *OFD1*, *MYO7A*, *USH1C*, *DFNB31*, *CDH23*, *PCDH15*, *USH1G*, *GPR98*, *BBS1-BBS10*, *TRIM32*, *BBS12*, *BBS13*, *AHI1*	adRP, arRP, xlRP, arLCA, JS, BBS, USH, xlCORD, xlCSNB, MKS, LGMD2H, MKKS
Photoreceptor structure	*RDS*, *ROM1*, *FSC2*	adRP, digenic RP, adMD
mRNA splicing	*HPRP3*, *PRPF8*, *PRPF31*, *PAP1*, *TOPORS*	adRP
Others	*ASCC3L1*, *SPATA7*,*EYS*, *KLHL7*, *RD3*, *KCNV2*, *RIMS1*, *CACNA2D4*, *ADAM9*, *CNNM4*, *TRPM1*, *CABP4*, *OFD1*	adRP, arRP, arCOD, arLCA, adCORD, CORD, arCORD, JS

adCORD: autosomal-dominant cone and rod dystrophy; adLCA: autosomal dominant Leber's congenital amaurosis; adMD: autosomal-dominant macular dystrophy; adRP: autosomal-dominant retinitis pigmentosa; arCORD: autosomal-recessive cone and rod dystrophy; arCOD: autosomal recessive cone dystrophy; arLCA: autosomal-recessive Leber's congenital amaurosis; arMD: autosomal-recessive macular dystrophy; arRP: autosomal-recessive retinitis pigmentosa; BBS: Bardet-Biedl syndrome; CORD: cone and rod dystrophy; dCSNB: dominant congenital stationary night blindness; FEVR: familial exhudative vitreoretinopathy; JS: Joubert syndrome; LGMD2H: limb and griddle muscular dystrophy type 2H; MD: macular degeneration; MKKS: McKusick-Kaufmann syndrome; MKS: Meckel-Gruber syndrome; RdCVF: rod-derived cone viability factor; RP: retinitis pigmentosa; USH: Usher syndrome; xlCORD: X-linked cone and rod dystrophy; xlCSNB: X-linked congenital stationary night blindness; xlRP: X-linked retinitis pigmentosa.

Table 5. Genes and proteins leading to retinal dystrophies involved in phototransduction, visual cycle and phagocytosis of rod outer segments

Gene	Location	Protein	Function	%	Type of RP
CNGA1	4p12	rod cGMP-gated channel alpha subunit	Phototransduction	2.2	arRP
CNGB1	16q13	rod cGMP-gated channel beta subunit	Phototransduction		arRP
GUCA1B	6p21.1	guanylate cyclase activating protein 1B	Phototransduction		adRP, adMD
RHO	3q22.1	rhodopsin	Phototransduction	19-25	adRP, arRP, dCSNB
PDE6A	5q33.1	cGMP phosphodiesterase alpha subunit	Phototransduction	4	arRP
PDE6B	4q16.3	cGMP phosphodiesterase beta subunit	Phototransduction	4	arRP, dCSNB
PDE6C	10q23.33	cone alpha subunit of cGMP phosphodiesterase	Phototransduction		arCOD
SAG	2q37.1	arrestin	Phototransduction		arRP, Oguchi disease
CNGB3	8q21.3	cone cyclic nucleotide-gated cation channel beta 3 subunit	Phototransduction		arCOD
ABCA4	1p22.1	ATP-binding cassette transporter - retinal	Visual cycle	2,9	arRP, arMD, arCORD
RGR	10q23.1	RPE-retinal G protein-coupled receptor	Visual cycle	0,5	arRP, coroid sclerosis
RLBP1	15q26.1	retinaldehyde-binding protein 1	Visual cycle		arRP
BEST1	11q12.3	Bestrophin-1	Visual cycle		adMD (Best type)
IRBP			Visual cycle		arRP
RPE65	1p31.2	retinal pigment epithelium-specific 65 kDa protein	Visual cycle	2	arRP, arLCA
CA4	17q23.2	carbonic anhydrase IV	Visual cycle		adRP
RDH12	14q24.1	retinal dehydrogenase 12	Visual cycle	4	arRP
IDH3B	20p13	NAD(+)-specific isocitrate dehydrogenase 3 beta	Visual cycle		arRP
ELOVL4	6q14.1	elongation of very long fatty acids protein	Visual cycle		adMD
PITPNM3	17p13.2	phosphatidylinositol transfer membrane-associated family member 3	Visual cycle		adCORD
LRAT	4q32.1	lecithin retinol acyltransferase	Visual cycle	0,7	arRP, arLCA
GUCY2D	17p13.22	retinal-specific guanylate cyclase 2D	visual cycle	21	arLCA, adCORD
MERTK	2q13	c-mer protooncogene receptor tyrosine kinase	Phagocytosis of ROS	0,6	arRP

adCORD: autosomal-dominant cone and rod dystrophy; adMD: autosomal-dominant macular dystrophy; adRP: autosomal-dominant retinitis pigmentosa; arCORD: autosomal-recessive cone and rod dystrophy; arCOD: autosonal recessive cone dystrophy; arLCA: autosomal-recessive Leber's congenital amaurosis; arMD: autosomal-recessive macular dystrophy; arRP: autosomal-recessive retinitis pigmentosa; ROS: reactive oxygen species.

Table 6. Genes and proteins leading to retinal dystrophies involved in structure of photoreceptors and ciliary function

Gene	Location	Protein	Function	%	Type of RP
CEP290	12q21.32	centrosomal protein 290 kDa	Structural: connecting cilium	21	arRP, arLCA, JS, BBS
FSC2	17q25.3	Fascin 2	Structural		adRP
RDS	6p21.2	Retinal degeneration slow-peripherin	Structural	9.5	adRP, adMD, RP digenic with ROM1
ROM1	11q12.3	retinal outer segment membrane protein 1	Structural	2	RP digenic with RDS
RP1	8q12.1	RP1 protein	Structural: photoreceptor trafficking	3.5	adRP, arRP
TULP1	6p21.31	tubby-like protein 1	Retinal development	2	arRP, arLCA
USH2A	1q41	usherin	Structural: photoreceptor trafficking	10	arRP, USH
CRB1	1q31.3	crumbs homolog 1	Structural: extracellular matrix	6.5	arRP, arLCA
RP2	Xp11.23	XRP2 protein similar to human cofactor C	Structural: photoreceptor trafficking	15	xlRP
RPGR	Xp14	retinitis pigmentosa GTPase regulator	Structural: photoreceptor trafficking	75	xlRP, xlCORD, xlCSNB
RPGRIP1	14q11.2	RP GTPase regulator-interacting protein 1	Structural: photoreceptor trafficking		arLCA
LCA5	6q14.1	Lebercilin	Structural: photoreceptor trafficking		arLCA
OFD1	Xp22.2	oral-facial-digital syndrome 1 protein	Ciliary function		JS
MYO7A	11q13.5	Myosin VIIA	Photoreceptor trafficking		USH
USH1C	11p14-p15	harmonin	Structural: scaffolding		USH
DFNB31	9q32-q34	whirlin	Structural: scaffolding		USH
CDH23	10q21-q22	cadherin-23	Structural: cell-cell adhesion		USH
PCDH15	10q21-q22	protocadherin-15	Structural: cell-cell adhesion		USH
USH1G	17q24-q25	SANS	Structural: scaffolding		USH
GPR98	5q14-q21	VLGR1	Structural: extracellular matrix		USH
BBS1	11q13	BBS protein 1	Ciliary function		BBS
BBS2	16q21.2	BBS protein 2	Ciliary function		BBS
ARL6/BBS3	3q11.2	ADP-ribosylation factor-like 6	Ciliary function		BBS
BBS4	15q24.1	BBS protein 4	Ciliary function		BBS
BBS5	2q31.1	flagellar apparatus-basal body protein DKFZp7621194	Ciliary function		BBS
MKKS/BBS6	20p12.1	McKusick-Kaufman syndrome protein	Ciliary function: chaperonine		BBS, MKKS
BBS7	4q27	BBS protein 7	Ciliary function		BBS
TTC8/BBS8	14q32.11	tetratricopeptide repeat domain 8	Ciliary function		BBS
B1/BBS9	7p14.3	parathyroid hormone-responsive B1 protein	Ciliary function		BBS
BBS10	12q21.2	BBS protein 10	Ciliary function: chaperonine		BBS
TRIM32	9q33.1	tripartite motif-containing protein 32	Ciliary function		BBS, LGMD2H
BBS12	4q27	BBS protein 12	Ciliary function: chaperonine		BBS
MKS1/BBS13	17q22	FABB proteome-like protein	Ciliary function		BBS, MKS
AHI1	6q23.3	Abelson helper integration site 1	Ciliary function		NPH

adMD: autosomal-dominant macular dystrophy; adRP: autosomal-dominant retinitis pigmentosa; arLCA: autosomal-recessive Leber's congenital amaurosis; arRP: autosomal-recessive retinitis pigmentosa; BBS: Bardet-Biedl syndrome; CORD: cone and rod dystrophy; JS: Joubert syndrome; LGMD2H: limb and griddle muscular dystrophy type 2H; MKKS: McKusick-Kaufmann syndrome; MKS: Meckel-Gruber syndrome; NPH: Nephrohophthisis;.RP: retinitis pigmentosa; USH: Usher syndrome; xlCORD: X-linked cone and rod dystrophy; xlCSNB: X-linked congenital stationary night blindness; xlRP: X-linked retinitis pigmentosa.

Phagocytosis of photoreceptor discs

The stacks of discs containing visual pigment molecules in the outer segments of the photoreceptors are constantly renewed. New discs are added at the base of the outer segment at the cilium, and old discs are displaced up the outer segment and engulfed by the apical processes of the pigment epithelium. They are then broken down by lysis. Photoreceptor outer-segment discs are phagocytosed by the pigment epithelium in a diurnal cycle. Among the different proteins involved in this process, only *MERTK*, the gene encoding c-mer proto-oncogene receptor tyrosine kinase, has been identified as causing arRP.

Table 7. Genes and proteins leading to retinal dystrophies involved in retinal development, mRNA splicing and other functions

Gene	Location	Protein	Function	%	Type of RP
KCNV2	9p24.2	potasium channel subfamily V member 2	Ion interchange		arCOD
IMPDH1	7q32.1	inosine monophosphate dehydrogenase 1	Nucleotide biosynthesis	2.5	adRP, adLCA
CRX	19q13.32	cone-rod otx-like photoreceptor homeobox transcription factor	Retinal development	1	adRP, adLCA, arLCA, adCORD
NRL	14q11.2	neural retina leucine zipper	Retinal development	0.7	adRP, arRP
NR2E3	15q23	nuclear receptor subfamily 2 group E3	Retinal development		arRP
EYS	6q12	eyes shut/spacemaker (Drosophila) homolog	Unknown		arRP
HPRP3	1q21.3	human homolog of yeast pre-mRNA splicing factor 3	mRNA splicing	1	adRP
PRPF8	17p13.3	human homolog of yeast pre-mRNA splicing factor C8	mRNA splicing	3	adRP
PRPF31	19q13.42	human homolog of yeast pre-mRNA splicing factor 31	mRNA splicing	8	adRP
PROM1	4p15.32	Prominin	Photoreceptor discs development		adCORD, adMD
SNRNP200	2q11.2	small nuclear ribonucleoprotein 200kDa	mRNA splicing		adRP
KLHL7	7p15.3	kelch-like 7 protein (Drosophila)	Protein degradation		adRP
TOPORS	9p21.1	topoisomerase I binding arginine/serine rich protein	mRNA splicing	1	adRP
RD3	1q32.3	protein: RD3 protein	Unknown		arLCA
RAX2	19p13.3	retina and anterior neural fold homeobox 2 transcription factor	Retina development		CORD
SEMA4A	1q22	Semaphorin 4A	Neuronal development		adCORD
RIMS1	6p13	regulating synaptic membrane exocytosis protein	Ribbon synapse trafficking		adCORD
CACNA2D4	12p13.33	calcium channel, voltage-dependent, alpha 2/delta subunit 4	Ribbon synapse trafficking		arCOD
CERKL	2q31.3	ceramide kinase-like protein			arRP
AIPL1	17q13.2	arylhydrocarbon-interacting receptor protein-like 1	Chaperone	3.4	arLCA, adCORD
PAP1	7p14.3	PIM-1 kinase	mRNA splicing		adRP
ADAM9	8p11.23	ADAM metallopeptidase domain 9 (meltrin gamma) protein	Structural: adhesion molecule		CORD
CNNM4	2q11.2	cyclin M4	Neural retina function		Jalili synd.
TRPM1	15q13.3	transient receptor potential cation channel, subfamily M, member 1 (melastatin)	Light-evoked response of the inner retina		adCSNB
SPATA7	14q31.3	spermatogenesis associated protein 7	Unknown		arLCA, arRP
TSPAN12	7q31.31	tetraspanin 12	Retinal development		FEVR
OTX2	14q22.3	orthodenticle homeobox 2 protein	Retinal development		adLCA
ASCC3L1	2q11.2	activating signal cointegrator 1 complex subunit 3-like 1	Unknown		adRP
CABP4	11q13.1	calcium binding protein 4	Synapsis function		arCORD
USH3A	3q21-q25	clarin-1	Ribbon synapse trafficking		USH

adCORD: autosomal-dominant cone and rod dystrophy; adCSNB: autosomal dominant congenital stationary night blindness adLCA: autosomal dominant Leber's congenital amaurosis; adMD: autosomal-dominant macular dystrophy; adRP: autosomal-dominant retinitis pigmentosa; arCOD: autosomal recessive cone dystrophy; arCORD: autosomal-recessive cone and rod dystrophy; arLCA: autosomal-recessive Leber's congenital amaurosis; arRP: autosomal-recessive retinitis pigmentosa; CORD: cone and rod dystrophy; FEVR: familial exhudative vitreoretinopathy; RP: retinitis pigmentosa; USH: Usher syndrome.

Retinal development

Retinal cells are specialized neurons structured in layers. Their patterns of connectivity are crucial, and the correct development of these cells is essential for retinal function. This development is regulated by the precise expression of genes in the right cell type and at the right time, and this regulation is mediated by the synergistic/antagonistic action of a limited number of transcription factors. Mutations in the cone-rod otx-like photoreceptor homeobox transcription factor (encoded by the gene CRX) are responsible for adRP, adLCA, arLCA and adCORD; mutations in the neural retina leucine zipper (encoded by the gene *NRL*) can lead to adRP and arRP. Mutations in the gene encoding the tubby-like protein 1 (*TULP1*) can cause recessive RP or LCA. *RAX2* encodes the retina and anterior neural fold homeobox 2 transcription factor, and mutations are responsible for CORD. Mutations in *NR2E3* encoding the nuclear receptor subfamily 2 group E3 cause arRP or adRP.

Mutations in the genes encoding prominin (*PROM1*) and semaphorin 4A (*SEMA4A*) lead to adCORD. *OTX2* (encoding orthodenticle homeobox 2 protein) mutations are associated with adLCA. Finally, defects in *TSPAN12* (tetraspanin 12) are associated with familial exudative vitreoretinopathy.

Photoreceptor structure

Although the majority of RD phenotypes appear to result from defects at a single genetic locus, at least one form of RP appears to require co-inheritance of defects in the unlinked genes *RDS*, which encodes peripherin/RDS, and *ROM1*, which encodes retinal outer-segment membrane protein 1. These proteins are components of the polypeptide subunits of an oligomeric transmembrane protein complex, which is present at photoreceptor outer-segment disc rims and is essential for the correct incidence of light into the discs.

Another protein, fascin 2, encoded by *FSC2*, appears to play a role in the assembly or stabilization of inner segment and calycal process actin filament bundles in photoreceptors and probably regulates the inner segment actin cytoskeleton.

Ciliary structure and function

Photoreceptors have an inner segment that contains the cell organelles and an outer segment composed almost exclusively of optic discs. The connecting cilium connects the inner and outer segments. These discs are constantly renewed and a high number of molecules must travel from the inner segment to the outer segment through the connecting cilium. The development and architecture of the connecting cilium, the correct folding of the involved proteins and the links between the cilium and its surrounding region (calycal process, extracellular matrix) have been shown to be essential for retinal function. Furthermore, as cilia are specialized structures present in many other tissues, defects in the protein components of the cilia and chaperones involved in their development can cause not only isolated RD but also conditions that include RD among their symptoms, such as USH or BBS. Recently, it has been demonstrated that some ciliary proteins act as positive or negative phenotypic modifiers on defects in other proteins. Some examples are: *USH2A*, which encodes the large extracellular protein usherin, and defects are responsible for arRP and USH; the genes *USH1C* and *DFNB31*, which encode the scaffolding proteins harmonin and whirlin; and *CDH23* and *PCDH15*, which encode the cell-cell adhesion proteins cadherin 23 and protocadherin 15, respectively.

mRNA splicing

Pre-mRNA splicing is a critical step in mammalian gene expression. Mutations in genes involved in the splicing processes or spliceosome are associated with a wide range of human diseases, including those involving the retina. Among the genes involved in mRNA splicing, mutations in *PRPC8* (human homolog of yeast pre-mRNA splicing factor C8), *PRP31* (human homolog of yeast pre-mRNA splicing factor 31), *HPRP3* (human homolog of yeast pre-mRNA splicing factor 3), *PAP-1* (PIM-1 kinase), *TOPORS* (topoisomerase-I-binding arginine/serine-rich protein) and *SNRNP200* (small nuclear ribonucleoprotein, 200 kDa) are associated with adRP [14-18], although the mechanisms behind the process remain unclear.

Other functions

Many other genes and proteins are associated with RD. These proteins have a wide spectrum of functions, such as degradation of proteins in the retinal pigmented epithelium (RPE), ionic interchange, trafficking of molecules in the ribbon synapse of photoreceptors and many others. In addition, the functions of some proteins that have been associated with RD are still unknown.

Molecular diagnosis in retinal dystrophies

The first step toward the diagnosis of RD at the molecular level is genotyping; this allows a more precise prognosis of the possible future clinical evolution of RD, and it can be followed by genetic counseling. Moreover, genetic testing is crucial for the inclusion in human gene-specific clinical trials aimed at photoreceptor rescue. However, genetic and phenotypic heterogeneity limit mutation detection, rendering molecular diagnosis very complex. While sequencing remains the gold standard, this is costly and time consuming, and so alternative diagnostic approaches have been recently implemented.

One such alternative diagnostic approach is the use of microarray platforms to detect RP mutations. The most widely used are the specific-disease chips for different types of RD. They contain the previously identified mutations on the responsible known genes Identification rates (identifying at least one disease-associated mutation) depend on the geographical origin and ethnicity of the patient, and they currently stand at 47 to 78% for Stargardt disease [19-23], 28 to 40% for CORD [21, 23, 24, 25], 28 to 46% for LCA [26,-30], 45% for USH 1, and 26% for USH 2 [31, 32]. These represent inexpensive and rapid first-step genetic testing tools for patients with a specific RD diagnosis.

In addition, other high-throughput DNA sequencing platforms targeted to hundreds of genes are being developed. They have been designed to contain either genes limited to exons [33] or full-length retinal disease genes, including introns, promoter regions or both [34]. Other chip-based co-segregation analyses for autosomal-recessive forms and LCA have also been designed, but

these analyses requires the inclusion of samples from all the members of the family, both healthy and affected [35, 36].

Indirect genetic tools for linkage analysis and/or homozygosity mapping are also being used for RD genotyping, mainly for research purposes. However, increasing availability and low costs have made homozygosity mapping a particularly appealing approach for the molecular diagnosis of RD [37].

The analytical validity of these procedures has been proved. However, their clinical validity remains to be established for every ethnic group, specific array and type of retinal disease. Clinical applications are also somewhat limited due to the fact that many RP genes are still unknown, and mutations may lie outside of commonly tested regions.

Perspectives for future therapeutics

Currently, optical and electronic devices are the only tools available to improve vision in some patients with RD. In the majority of cases, there are no effective therapies available to prevent, stabilize or reverse monogenic RD.

A key goal in developing an effective therapy for RD is the understanding of its pathophysiology, and the identification of the molecular events and disease mechanisms occurring in the degenerative retina. Based on advances in knowledge about these processes, several novel therapeutic strategies are currently being evaluated, including pharmacological treatments, gene therapy and cell therapy.

RD disorders are initiated by mutations that affect rod and/or cone photoreceptors and cause subsequent degeneration and cellular death. Consequently, therapeutic strategies are focused on targeting the specific genetic disorder (gene therapy), slowing or stopping photoreceptor degeneration or apoptosis (growth factors or calcium-blocker applications, vitamin supplements, endogenous cone viability factors), or even the replacement of lost cells (transplantation, use of stem or precursor cells).

Before these strategies can be applied to humans, animal models, preclinical studies and appropriately designed human clinical trials are needed to test different treatments and provide information on their safety and efficacy. According to the ClinicalTrials.gov database, 44 interventional clinical trials for RP have been or are being carried out [38].

Pharmacological therapies

Developing an effective pharmacological therapy for RD must be based on the knowledge of the molecular events and major disease mechanisms and the extent to which they overlap. Current therapies target these pathogenic mechanisms.

Vitamin supplementation and chaperone treatments

Results from experimental effects on animal models [39] and a randomized controlled double-masked clinical trial [40] have suggested possible clinical benefits of vitamin A supplementation in RP. However, the use of these supplements in other genetic forms of RD, such as *ABCA4*-related diseases (arRP, arCORD, and autosomal-recessive Stargardt MD), may accelerate the accumulation of toxic lipofuscin pigments in the retinal pigment epithelium, and thus worsen photoreceptor degeneration. As a result, avoidance of vitamin A supplementation is recommended for people with Stargardt disease.

Another viable approach to RP therapy is the use of pharmacological chaperones [41]. Pharmacological chaperones target protein structure, while chaperone inducers (for example, geldanamycin, radicicol and 17-AAG) and autophagy inducers (for example, rapamycin) stimulate degradation, manipulating the cellular quality control machinery. Some studies have suggested that the rod opsin chromophore (11-cis retinal) and retinal analogues (for example, 9-cis retinal) can act as pharmacological chaperones, whereas rapamycin is effective against the toxic gain of function, but not the dominant-negative effects of mutant rod opsin [41].

Anti-apoptotic therapy and neuroprotection: endogenous cone viability factors and growth factors

The key goals in pharmacological therapy for RD are neuroprotection and the inhibition of pro-apoptotic pathways, or the activation of endogenous anti-apoptotic signaling systems [42]. Neuroprotection of photoreceptor cells is primarily targeted at structural preservation, and also preventing loss of function. The neuroprotective factors include one 'survival' factor (rod-derived cone viability factor (RdCVF)) and four different neurotrophic factors (ciliary neurotrophic factor, basic fibroblast growth factor, brain-derived neurotrophic factor and nerve growth factor) that delay rod degeneration in some animal models of RP [43].

RdCVF is a protein that increases cone survival. Injections of this protein in p.P23H rats induced an increase in cone cell number and a further increase in the electroretinogram, indicating that RdCVF can not only rescue cones but can also significantly preserve their function [44].

Ciliary neurotrophic factor has shown efficacy in different animal models, and has progressed to phase II/III clinical trials in early-stage and late-stage RP [45]. It has been administered by encapsulated cell technology, which allows the controlled, continuous and long-term administration of protein drugs in the eye, where the therapeutic agents are needed, and does not subject the host to systemic exposure [46].

Gene-based therapy

Many RD-associated genes have been identified and their functions elucidated. Over the past decade, there has been a substantial effort to develop gene therapy for inherited retinal degeneration, culminating in the recent initiation of clinical trials.

A variety of monogenic recessive disorders could be amenable to treatment by gene replacement therapy through the delivery of healthy copies of the defective gene via replication-deficient viral vectors [47, 48]. Preliminary results from three clinical trials indicate that the treatment of a form of LCA by gene therapy can be safe and effective. Phase I clinical trials of gene therapy targeting the gene *RPE65* [49-51] are being conducted in three different medical centers: Moorfields Eye Hospital, UK [49], the Children's Hospital of Philadelphia, USA, [51], and the Universities of Pennsylvania and Florida, USA. [50],

For some autosomal-dominant forms of RP or LCA, in which expression of a mutant allele has a gain-of-function effect on photoreceptor cells, or a dominant-negative mechanism or a combination of both, gene therapy is likely to depend on efficient silencing of the mutated allele [52]. Gene-silencing strategies for these conditions include RNA interference by microRNA-based hairpins (Prph2 animal model), short hairpin RNAs (*IMPDH1* gene murine model), RNA interference by microRNA combined with gene replacement (transgenic mouse simulating human RHO-adRP), and antisense oligonucleotide technologies.

Cell therapy

Adult stem cells isolated from the retinal pigment epithelium at the ciliary body margin can differentiate into all retinal cell types, including photoreceptors, bipolar cells and Müller glia. Animal experiments have shown that, in response to environmental cues, they can repopulate damaged retinas, regrow neuronal axons, repair higher cortical pathways, and restore pupil reflexes, light responses and basic pattern recognition. When transplanted into a damaged retina, the progenitor cells integrate with the retina, forming a protective layer that preserves existing cells and increases photoreceptor density - that is, neurogenesis can be fostered by recruitment of endogenous stem cells into damaged areas or by transplanted stem cells [53].

Clinical trials using human fetal neural retinal tissue and retinal pigment epithelium cells and adult stem cells are in progress. A phase I clinical trial to repair damaged retinas in 50 patients with RP and age-related macular degeneration has been conducted in India. Phase I clinical trials to repair damaged retinas in patients with RP degeneration have been conducted using autologous stem cells derived from bone marrow, injected either near the cornea or intravitreally (ClinicalTrials.gov NCT01068561). Preliminary results have shown visual improvement.

Additionally, a non-invasive cell-based therapy consisting of systemic administration of pluripotent bone-marrow-derived mesenchymal stem cells to rescue vision and associated vascular pathology has been tested in an animal model for RP, resulting in preservation of both rod and cone photoreceptors and visual function [54]. These results underscore the potential application of mesenchymal stem cells in treating retinal degeneration.

Concluding remarks

To date, more than 200 genes associated with RD have been identified; they are involved in many different clinical entities such as RCA, LCA, USH, CORD and MD. The most surprising outcome of these findings is the exceptional heterogeneity involved: a high number of disease-causing mutations have been detected in most RD genes, mutations in many different genes can cause the same disease, and different mutations in the same gene may cause different diseases. This genetic heterogeneity underlies a high clinical variability, even among family members with the same mutation. The RD genes involve many different pathways, and expression ranges from very limited (for example, expressed in rod photoreceptors only) to ubiquitous.

Gaining knowledge of the genetic causes and pathways involved in the photoreceptor degeneration underlying these disorders is the first step in implementing the correct clinical management and a possible prevention or cure for the disease.

An increasing number of clinical trials are exploring different therapeutic approaches with the aim of treating inherited retinal dystrophies. Phenotypic characterization and genotyping are crucial in order to provide patients with potential personalized treatment. Further research into the mechanisms underlying photoreceptor degeneration and retinal cell apoptosis should also bring us closer to the goal of developing efficient and safe therapies.

Abbreviations

ad: autosomal dominant; adCORD: autosomal-dominant cone and rod dystrophy; adLCA: autosomal dominant LCA; adMD: autosomal-dominant macular dystrophy; adRP: autosomal-dominant retinitis pigmentosa; ar: autosomal-recessive; arCORD: autosomal-recessive cone and rod dystrophy; arLCA: autosomal-recessive LCA; arMD: autosomal-recessive macular dystrophy; arRP: autosomal-recessive retinitis pigmentosa; BBS: Bardet-Biedl syndrome; CORD: cone and rod dystrophy; dCSNB: dominant congenital stationary night blindness; FEVR: familial exhudative vitreoretinopathy; JS: Joubert syndrome; LCA: Leber's congenital amaurosis; LGMD2H: limb and griddle muscular dystrophy type 2H; MD: macular degeneration; MKKS: McKusick-Kaufmann syndrome; MKS: Meckel-Gruber syndrome; RD: retinal dystrophy; RdCVF: rod-derived cone viability factor; ROS: reactive oxygen species; RP: retinitis pigmentosa; USH: Usher syndrome; xl: X-linked; xlCORD: X-linked cone and rod dystrophy; xlCSNB: X-linked congenital stationary night blindness; xlRP: X-linked retinitis pigmentosa.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
CA designed the overall layout and different sections of the article, and wrote the first draft of the manuscript. JM performed a thorough review of the manuscript, and provided the descriptions of the candidate genes and pathways, and the genetic patterns. Both authors reviewed and approved the final manuscript.

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