

2015

Retinitis Pigmentosa: A Brief Review of the Genetic and Clinical Aspects of the Disease

Itia Dowdell

Follow this and additional works at: <https://digitalcommons.library.uab.edu/inquiro>



Part of the [Higher Education Commons](#)

Recommended Citation

Dowdell, Itia (2015) "Retinitis Pigmentosa: A Brief Review of the Genetic and Clinical Aspects of the Disease," *Inquiro, the UAB undergraduate science research journal*: Vol. 2015: No. 9, Article 23.
Available at: <https://digitalcommons.library.uab.edu/inquiro/vol2015/iss9/23>

This content has been accepted for inclusion by an authorized administrator of the UAB Digital Commons, and is provided as a free open access item. All inquiries regarding this item or the UAB Digital Commons should be directed to the [UAB Libraries Office of Scholarly Communication](#).

Retinitis Pigmentosa: A Brief Review of the Genetic and Clinical Aspects of the Disease

Itia Dowdell

Science and Technology Honors Program, University of Alabama at Birmingham, Birmingham, AL, USA

School of Health Professions Honors Program, University of Alabama at Birmingham, Birmingham, AL, USA

Department of Clinical and Diagnostic Sciences, University of Alabama at Birmingham, Birmingham, AL, USA

ABSTRACT

Retinitis Pigmentosa (RP) is a heterogeneous set of inherited retinal diseases that affects 1 in 3,000–7,000 people worldwide. Typical onset is from 10–30 years old and most forms are progressive, often leading to blindness. Defects in more than 200 genes have been identified that cause RP. The disease is characterized as a progressive rod-cone dystrophy that presents with night blindness, loss of peripheral vision, waxy pallor of the optic disc, pigmentary changes, and a reduced visual field. There are different modes of transmission of RP: autosomal dominant (ADRP), autosomal recessive (arRP), X-linked (XLRP) and mitochondrial. The genetics behind the different forms of RP and the degree of severity vary, although some overlap, thus contributing to the difficulty of differential diagnosis. RP can manifest either as a non-syndromic disease, or as part of a syndrome, such as in Usher's syndrome (hearing and vision loss) and Bardet-Biedl syndrome (a ciliopathy). The purpose of this review is to summarize the major genetic and molecular findings, as well as the diseases, associated with RP. Due to space limitations, this review is not fully comprehensive.

Keywords: Retinitis pigmentosa, non-syndromic retinitis

pigmentosa, rod-cone dystrophy, rhodopsin

INTRODUCTION

Retinitis pigmentosa (RP) is a heterogeneous set of inherited retinal diseases. RP affects 1 in 3,000–7,000 individuals worldwide and is characterized by a primary loss of night and peripheral vision as a result of rod photoreceptor cell degeneration^{1,2}. Central vision is often lost as the cone photoreceptor cells degenerate, consequently causing progressive degeneration of the macula and fovea as well¹. This degeneration can be a result of the disease itself or secondary to the rod cell degeneration¹. RP is also characterized by atrophy in the pigment epithelium and outer retina, RPE cell migration into the retina, reduced visual field, waxy pallor of the optic disc, abnormal or absent a- and b-waves on an electroretinogram (ERG), and an abnormal fundus with bone cell spicule deposits as a result of cell apoptosis³.

RP can occur either as part of a syndrome or in a non-syndromic fashion. There are several forms of this disease due to mutations in different genes and to different mutations within the same gene with each varying in age of onset,

severity, and mode of inheritance⁴. Autosomal Dominant RP (ADRP) is usually the mildest form of the disease, with patients maintaining relatively good visual acuity until the sixth decade³. Autosomal Recessive RP (arRP) is the most prevalent form of the disease, accounting for 50–60% of cases⁵. RP can also occur in an isolated form in which the patient has no family history of the disease, but even in these cases, parental contributions of defective genes can be established. There are also rarer forms of the disease such as mitochondrial, digenic, and X-linked (XLRP). XLRP has the most severe phenotype, accounting for 10–15% of RP cases¹. Visual acuity is usually severely impaired by the fourth decade¹. Onset of RP usually occurs in adolescence or young adulthood, but in cases of congenital RP, patients can be diagnosed with Leber Congenital Amaurosis (LCA), a largely autosomal recessively inherited retinal dystrophy that is usually diagnosed prenatally⁶. LCA is one of the most frequent causes of childhood blindness, accounting for 10–20% of cases⁶. It also accounts for approximately 5% of RP cases⁶.

There are at least 56 genes that have been confirmed to be associated with non-syndromic RP, with more than 3,100 associated mutations⁴. With recently developed technology, for example, next generation sequencing (NGS), 30–80% of mutations in patients can now be identified². NGS has led to the discovery of more mutant genes and has become a novel technique for possible molecular diagnosis of the disease².

Autosomal Dominant Retinitis Pigmentosa (ADRP)

To date, 23 genes have been found to be associated with ADRP². Molecular diagnosis is becoming a more feasible idea with the recent development of a DNA array that is able to detect up to 385 mutations in 16 of the known causative ADRP genes¹. The following genes are those that are responsible for the highest percentages of RP cases (see Table 1).

RHO

The *RHO* gene encodes the opsin protein, the protein portion of a molecule that, with its chromophore, 11-*cis* retinal, is responsible for initiating the phototransduction cascade within the rod photoreceptor cells, an enzymatic cascade that is crucial for vision. Mutations in this protein are responsible for 26.5% of all RP cases and 30–40% of ADRP cases¹. More than 100 mutations have been associated with this gene, with the more detrimental mutations resulting in protein misfolding, mis-trafficking, 11-*cis* retinal binding impairment and/or G-protein coupling/activation impairment¹. There are two classes of mutations: Class I and Class II⁷. Class I mutations are naturally occurring mutations that have similar expression levels, 11-*cis* retinal relationship, and plasma membrane association to the wild-type (WT) rhodopsin⁷. Most of these mutations are found at the C-terminal end of the protein, with the entire class being responsible for 15% of ADRP

mutations⁷. Class II mutations, in contrast, exhibit lowered expression levels, impaired 11-*cis* retinal binding and plasma membrane association, although the primary issue with this class is protein mis-folding⁷. This class is also responsible for 85% of ADRP mutations⁷.

Peripherin-2/RDS

The peripherin-2 gene (*PRPH2*), also called *RDS* for the mouse mutant retinal degeneration slow (*RD2*), encodes a 39-kDa intermembrane glycoprotein which localizes to the outer segment (OS) discs of rod and cone cells and is important in disc morphogenesis and stabilization¹. Sub-retinal injection of the *PRPH2* transgene through adeno-associated virus (AAV) into the *Prph2*^{RD2/RD2} mouse model resulted in restoration of the structural integrity of the photoreceptor layer, stabilization of OS generation, new disc formation and improved ERG a- and b-waves, which were originally undetectable by the second month of life in this model⁸. Mutations in this gene account for about 5–9.5% of ADRP cases¹.

RP1

The *RP1* gene codes for the 240-kDa retinal-photoreceptor specific ciliary protein, Retinitis Pigmentosa 1^{1,9}. Mutations in this gene account for 5–10% of all ADRP cases, including 4% of cases in the U.S.¹ These mutations cause both dominant and recessive RP¹. The RP1 protein is expressed in both rod and cone photoreceptor cells in which it localizes to the axoneme of the connecting cilium (CC) and OS in mice. RP1 affects photosensitivity of the cell, assembly and stabilization of microtubules¹⁰. Mouse models, the *rp1*^{-/-} for example, have shown that upon disruption of RP1, OS mis-alignment and dysplasia occur¹⁰. Mutations in this gene result in variable onset and severity of the disease, most likely due to genetic modifiers or environmental influences¹. In general, however, heterozygous inheritance does result in a milder phenotype and later onset, as compared to homozygous inheritance, which results in earlier onset and a more severe phenotype¹⁰.

Autosomal Recessive Retinitis Pigmentosa (arRP)

To date, 37 genes have been found to be associated with arRP². Molecular tests for mutation screening are now able to detect 594 mutations in at least 20 of the associated genes¹. *RPE65*, *USH2A* and *PDE6* genes can now be fully sequenced at the DNA level¹. Most mutations are rare and cause 1% or fewer of cases¹. The following mutations account for a more prevalent percentage of cases (see Table 1).

RPE65

This gene codes for an isomerohydrolase that is found in the retinal pigment epithelium (RPE)². Isomerohydrolase is thought to play a role in the regeneration of 11-*cis* retinal from all-*trans* retinal when all-*trans* retinyl ester is converted to 11-*cis* retinol, which is a critical step in this enzymatic conversion¹¹.

This process is important because the protein portion of rhodopsin needs to be able to bind to its chromophore, 11-*cis* retinal, in order to form the conformation necessary for the conduction of the phototransduction cascade¹¹. There are over 60 mutations associated with this gene¹. There are a good number of relevant animal models, which has resulted in the disease mechanism of this mutation being better understood¹. For example, *RPE65*-deficient mice are found to have a build-up of retinyl esters and other intermediates of the visual cycle in the RPE¹². Sub-retinal injection of a human *RPE65* cDNA cassette using recombinant adeno-associated virus (rAAV) into *RPE65*^{-/-} purebred Briard dogs also showed a restoration of visual function in the treated retina of these animals¹.

PDE6

The heterotrimeric phosphodiesterase 6 (PDE6) complex regulates the intracellular levels of cGMP in the OS of the rod and cone cells by hydrolyzing it in response to the G-protein, Transducin, activation initiated by rhodopsin¹. There are four subunits: two catalytic subunits, alpha and beta, and two inhibitory gamma subunits. Defects in all three genes have been identified that cause arRP¹. Low levels of the alpha and beta subunits have a possible link to rod and cone cell degeneration¹. PDE6 inactivation is also associated with an excessive influx of Ca²⁺; this is thought to be a possible cause of rod cell apoptosis, but the use of Ca²⁺ blockers to reduce this effect in the *PDE6b*^{rd1}/*PDE6b*^{rd1} mouse and the Irish setter dog models have yielded inconsistent results¹. Interestingly, the protein responsible for synthesizing cGMP, guanylate cyclase (GC1), does not cause any forms of RP, except recessive Leber Congenital Amaurosis (LCA-1) and cone-rod dystrophy (CORD6)¹³.

Mutations in these two genes are the second most identifiable causes of arRP, with mutations in *USH2A* being the first¹. Complex mutations in the PDE6 alpha and beta subunit genes are also responsible for 8% of all diagnosed cases of arRP¹.

X-linked Retinitis Pigmentosa (XLRP)

Ten to fifteen percent of patients with RP are diagnosed with XLRP, presenting with a severe phenotype early in the disease¹. This condition can also occur in females, although these cases are usually milder compared to the condition in male populations¹. These cases are usually due to a non-random or skewed inactivation of an X chromosome¹. Six gene loci have been located, although only three genes to date have been found to be associated with XLRP¹. Oral facial digital syndrome type 1 (OFD1) gene mutations are X-linked dominant and result in primary cilia dysfunction and embryonic lethality in males^{1,14}.

RPGR/RP3

The Retinitis Pigmentosa GTPase Regulator (*RPGR*) gene undergoes complex splicing to yield multiple isoforms that localize to the rod outer segment (ROS) and are essential for cell viability¹⁵. There are two isoforms that are the main focus of study since they are the most widely expressed: the *RPGR*^{ORF15}, primarily associated with primary cilia, localizing to the OS and connecting cilium (CC) of photoreceptors, and *RPGR*¹⁻¹⁹, which localizes to the endoplasmic reticulum¹⁵. Mutations on the C-terminus of *RPGR*^{ORF15} are the most relevant as they cause XLRP3, the most severe form of RP¹⁶. XLRP3 also accounts for 14% of all RP cases¹⁶. Discovering more about the localization and physiological effects of the isoforms are critical for determining more about the disease mechanism¹⁶. Mutations in this gene are the principal cause of XLRP, accounting for mutations in 70% of patients¹⁶.

RP2

The *RP2* gene product is predicted to be homologous with human cofactor C, which is involved in the terminal step of beta tubulin folding; mutations result in an accumulation of misfolded proteins¹. In patients, missense mutations and other mutations that can lead to truncated proteins have been found throughout the coding region. *RP2* and *RPGR* together are responsible for over 80% of XLRP clinical cases which together with their associated pathology makes them good candidates for small molecule or gene therapy¹.

Table 1 | Genes, gene products and functions of important proteins that cause non-syndromic RP.

Abbreviations: RP, retinitis pigmentosa. ADRP, autosomal dominant retinitis pigmentosa. arRP, autosomal recessive retinitis pigmentosa. XLRP, X-linked retinitis pigmentosa.

Types of RP	Gene	Gene Product	Percentage of cases	Function	References
ADRP	RHO	Rhodopsin	30-40%	Phototransduction	1
	PRPH2	Peripherin-2	5-9.5%	Photoreceptor outer segment structure	1
	RP1	Retinitis Pigmentosa 1	5-10%	Photosensitivity, assembly and stabilization of microtubules	1, 10
arRP	RPE65	Retinal pigment epithelium-specific 65kDa protein	2%	Production of 11- <i>cis</i> -Vitamin A	4
	PDE6	Phosphodiesterase 6	8%	cGMP hydrolysis	1
XLRP	RPGR	Retinitis pigmentosa GTPase regulator	70%	Cell viability	1,4
	RP2	Retinitis Pigmentosa 2	10%	Involved in beta-tubulin folding	1,4

Syndromic RP

RP can also occur concomitantly with systemic disease, with the symptoms, age of onset, and severity varying with the particular disease. The two of focus in this review are

Usher's syndrome and Bardet-Biedl syndrome (BBS), two diseases under the classification of a group of diseases called ciliopathies. One note to make, however, is that although Usher's syndrome can be considered a ciliopathy based on the fact that its interactome is linked with the proteins of other ciliopathies, it is not exclusively a ciliopathy¹⁷. This group of diseases is characterized by dysfunction in relation to the primary cilia, with most of the diseases presenting with system-wide pathology in addition to RP. Usher's syndrome and BBS are the most common of the ciliopathies with over 1,200 mutations associated with these diseases².

Bardet-Biedl Syndrome (BBS)

Bardet-Biedl Syndrome (BBS) is a rare disease that affects 1:100,000–1:160,000 worldwide^{18,19}. It is an autosomal recessive disease, although one case of triallelic (three genes involved) inheritance has been reported^{18,20}. BBS is one of the major causes of syndromic retinal dystrophy, accounting for over 90% of cases²¹. BBS can be characterized by cone-rod, rod-cone and/or choroid dystrophy, although rod-cone dystrophy in the form of RP is the most common and often used as a means of diagnosis^{18,21}. Truncal obesity, intellectual disability, post-axial polydactyl and renal abnormalities are several other signs of the disease¹⁸. The renal abnormalities cause the most complications with the disease, increasing the morbidity of the disease as well as the mortality rate¹⁸. Night blindness often occurs around 7–8 years of age causing the patient to generally be classified as legally blind after 15.5 (mean) years with the disease¹⁸. Overall, the phenotype and onset of the disease are highly variable²¹.

BBS Genetics

The gene products associated with the BBS genes are proteins that localize to the ciliary axoneme and basal body, involved in cilia biogenesis and maintenance of ciliary function¹⁸ (see Table 2). There are 17 genes that are associated with the disease, although those only account for approximately 80% of diagnoses, indicating that there are more genes and/or mutations to be identified to account for the other 20%^{4,18}. Pathogenic variants in the BBS genes 1–14 are known to be associated with the disease, whereas pathogenic variants in BBS genes 15–19 are suspected to be associated with the disease¹⁸. BBS1, 2, 4, 5, 7, 8 and 9 make up what is called the BBSome, a protein complex thought to be involved in ciliary targeting¹⁸. There is also a chaperonin complex associated with the BBSome made up of BBS6, 10 and 12¹⁸.

Animal Models

There are quite a few animal models that are used to study this syndrome, but one difficulty is generating or finding a model that accurately models the human phenotype. One animal model that has shown promise is the *Bbs1*^{M390R} mouse model, which specifically models the common human mutation²⁰.

There has been a genotype-phenotype correlation established with this model, with a milder phenotype being associated with this mutation²⁰. The model exhibits retinal degeneration, male infertility, and obesity due to hyperphagia, similarly to what is exhibited in human patients²⁰. Animal models have also given some insight into possible mechanisms underlying the disease. For example, the mouse model that is null for *BBS2*, 3, and 4 expressed a resistance to leptin activity, which may reveal an underlying mechanism for the obesity that is characteristic of BBS patients²⁰.

Table 2 | List of the gene product and function, if known, of BBS genes.

BBS, Bardet-Biedl syndrome.

	Gene	Gene Product	Gene Function	References
<i>BBS</i>	BBS1	BBS1 protein	Unknown function; possible ciliary function	4, 18
	BBS2	BBS2 protein	Unknown function; possible ciliary function	4, 18
	BBS3/ ARL6	ADP-ribosylation like factor 6	Unknown function; possible ciliary function	4, 18
	BBS4	BBS4 protein	Similar to O-linked N-acetylglucosamine transferases; possible ciliary function	4, 18
	BBS5	Flagellar apparatus-basal body protein DKFZp7621194	High conservation in flagella and cilia; possible ciliary function	4, 18
	BBS6/ MKKS	McKusick-Kaufman Syndrome protein	Protein sequence is similar to chaperonins; ciliary function	4, 18
	BBS7	BBS7 protein	Unknown function	4
	BBS8/TTC8	Tetratricopeptide repeat domain 8	Localizes to ciliary structures; interacts with PCMI, a protein involved in ciliogenesis	4, 18
	BBS9	Parathyroid hormone-responsive B1 protein	Unknown function	4, 18
	BBS10	BBS10 chaperonin	Possible role in planer cell polarity	4, 18
	BBS11	TRIM32	Tripartite motif-containing protein 32	4, 18
	BBS12	BBS12 protein	Type II chaperonin family	4, 18
	BBS13/ MKS1	Meckel syndrome type 1 protein	Component of flagellar basal body	4, 18
	BBS14/ CEP290	Centrosomal protein 290 kDa	Associates with microtubule proteins in centrosomes and cilia	4, 18
	BBS15/ WDPCP	WD repeat-containing planar cell polarity effector	Involved in planar cell polarity in embryogenesis; may affect ciliogenesis	4, 18
	BBS16/ SDCCAG8	Serologically-defined colon cancer antigen 8	Localizes to centrioles	4, 18
	BBS17/ LZTFL1	Leucine zipper transcription factor like-1	Negative regulator of BBSome; affects ciliary trafficking	4, 18
BBS18/ BBIP1	BBSome interacting protein 1	Member of BBSome complex	4, 18	
BBS19/ IFT27	Intraflagellar transport 27 <i>Chlamydomonas</i> homolog	Associated with intraflagellar transport in green algae	4, 18	

Diagnosis

The criteria for diagnosis is that at least four of the main manifestations, some of which are mentioned above, along with two secondary manifestations are identified in the patients^{18, 20}. Secondary manifestations can include Diabetes Mellitus (DM), speech disorders, congenital heart disease, dental anomalies and/or ataxia¹⁸. Differential diagnosis is often an issue with this syndrome as many of the manifestations can arise singularly and do not necessarily indicate BBS¹⁸. There are no treatments for this disease, only management of symptoms and the associated complications, such as monitoring blood sugar for DM management¹⁸.

Usher's Syndrome (US)

Usher's syndrome is an autosomal recessive disease that is the most frequent cause of deaf-blindness, accounting for over 50% of those with inherited deaf-blindness diseases²². This disease affects 3–6.2 per 100,000 individuals worldwide²². There are three subtypes of the disease, each varying in severity and onset, and characterized by congenital deafness, retinal degeneration, and varying degrees of vestibular function²². The first subtype is the most devastating, characterized by severe to profound congenital deafness, followed by pre-pubertal retinal degeneration and no vestibular function^{22,23}. Another subset of this type, Usher 1B, is caused by a mutation in the *MYO7A* gene²³. This form accounts for approximately 50% of Usher 1 cases and also has bi-allelic mutations associated with Usher type 2^{23,24}. The product encoded by this gene is also required for normal localization and function of RPE65²⁵.

The second sub-type is characterized by moderate to severe congenital hearing loss, pre- or post-pubertal RP onset, and, unlike the other two sub-types, these patients still have vestibular function present^{22,26}. This subtype accounts for over half of all Usher cases²².

Sub-type 3 is the rarest, characterized by progressive hearing loss, either pre- or post-lingual, variable onset of RP and variable vestibular function^{22,27}.

Genetics

To date, there are ten genes associated with Usher's syndrome²². There are six genes associated with Usher 1: *MYO7A* (USH1B), *USH1C*, *CDH23* (USH1D), *PCDH15* (USH1F), *USH1G*, and *CIB2* (USH1J)²² (see Table 3). There are three genes associated with Usher 2: *USH2A*, *GPR98* (USH2C), and *DFNB31* (USH2D)²². There are three other genes proposed to be associated with the disease as well, but have yet to be confirmed²². Defects in the *USH2A* gene are responsible for the majority of Usher 2 cases and have been associated with recessive non-syndromic RP²². Defects in this gene are also responsible for some cases of atypical Usher syndrome, those cases that do not fall into the subtypes and categories listed above²². *CLRN1* is the only gene associated with Usher 3 syndrome²². These genes are a part of what is called the Usher-interactome, a complex of proteins known to participate in common pathways in the retina and inner ear²². Most of the Usher 1 and 2 genes are a part of this complex, involved in localization of proteins in the stereocilia, hair bundle of inner ear cells, and periciliary areas of photoreceptors²². In the ear, these proteins are involved in the development and cohesion of the hair bundle cells in the cochlea and vestibular organ²². In the retina, these proteins act as support in the membrane junction between the inner segment (IS) and the CC²². They also play a role in the control of vesicle docking and cargo handover in the periciliary ridge.

	Gene	Gene Product	Gene Function	References
US Type 1	MYO7A (USH1B)	Myosin VIIA	Actin-based motor protein	4, 23
	USH1C	Harmonin	PDZ-domain protein	4, 23
	CDH23 (USH1D)	Cadherin23	Adhesion protein	4, 23
	PCDH15 (USH1F)	Protocadherin15	Adhesion protein	4, 23
	USH1G/ SANS	Human homolog of mouse scaffold protein containing Ankyrin repeats and SAM domain	Scaffold	4, 23
	CIB2 (USH1J)	Calcium and integrin binding family member 2	Calcium and integrin binding	4
US Type 2	USH2A	Usherin	Transmembrane linkage	4, 23
	GPR98 (USH2C)	VLGR1	G-protein coupled Receptor	4, 23
	DFNB31 (USH2D)	Whirlin	PDZ-domain protein	4, 23
US Type 3	CLRN 1 (USH3A)	Clarin 1	Possible role in hair and photoreceptor cell synapses	4

Table 3| List of the gene product and function of US genes. US, Usher's syndrome.

Animal Models

Some animal models of Usher Syndrome are available, for example the *Shaker1* mouse model which expresses the phenotype of vestibular dysfunction²⁸. However, an issue with mouse models is that they do not adequately express the retinal degeneration that is characteristic of this syndrome²⁸. Fish models somewhat compensate for this by not only expressing vestibular dysfunction, but also expressing retinal degeneration and diminished ERG amplitudes, indicative of a defect in photoreceptor response²⁸. *Orbiter*, a fish model, has aided in the discovery that the *pcdh15b* gene is important in OS organization and retinal function²⁸. Though fish models express these phenotypes and are able to teach us more about the syndrome, the scope to which fish models can be utilized is limited due to uncertainty of how representative they are of the human model since the genes may not be well conserved²⁸.

Diagnosis

Diagnosis is difficult with this disease, specifically differential diagnosis, because many of the symptoms can be misconstrued to be other ciliopathies, such as BBS²⁷. Genes like *USH2A* and *CLRN1* mutations are not only involved in the development of Usher's syndrome, but have also been associated with isolated cases of arRP, further contributing to the difficulty of differential diagnosis²⁷. Genetic testing for diagnosis is not applicable since the heterogeneity of the disease prevents genotype-phenotype correlations from being made²⁷. The proteins also have multiple functions and are even involved in non-syndromic cases of hearing loss and RP as well²⁷. There is, however, novel technology being developed for clinical practice; for example, there is now a DNA microchip available that is able to identify 30–50% of mutations in those affected by the disease²⁷.

There is currently no treatment available, only management of symptoms²⁷. Hearing aids and cochlear implantation are a few

of the methods utilized to manage the progressive hearing loss²⁷. There are currently no cures for RP, and techniques such as gene therapy, damaged cell replacement and vitamin supplementation to stop or slow degeneration and apoptosis are proposed ideas²⁷. The lack of animal models, pre-clinical studies and human trials has prevented these methods from being utilized clinically²⁷.

Gaps and Future Directions

Even though there has been great progress in discovering more about this disease, several gaps still exist in the available literature. Although new technology, such as NGS, is making it more effective to discover new genes and their function, determining what they contribute to the molecular and clinical manifestations of the disease is a challenge that cannot be quickly overcome. Deciphering the genotype-phenotype correlations is one of the major issues, since one gene mutation can lead to multiple diseases, as is the case for mutations in the *RHO* gene, which can result in ADRP, arRP or Congenital (stationary) Night Blindness (CNB)¹. Other genes can exhibit intra- and inter-familial phenotypic variability and incomplete penetrance, further contributing to the difficulty in discerning the underlying cause of the disease². Phenocopies (non-genetic causes of an RP phenotype) represent another complication in the characterization and management of the disease.

In terms of clinically applying the growing pool of information on this disease, there are issues with translating what is discovered in the lab to a format that can be efficiently and accurately interpreted by physicians. Because of the genotype-phenotype correlation discrepancies, there also can be conflicting results between what is diagnosed clinically and molecularly. Certain tests have been proposed to resolve these issues, such as functional assays, which could aid in determining the pathogenic effects of some of the genes, but as of now, it is too in-depth of a tool for clinical practice since there has been no database developed to filter and organize the results¹.

Despite these obstacles, research is progressing at a fast pace in terms of discovering more about this disease, and this knowledge is being translated to the clinics, albeit at a slower pace. For example, one of the first successful gene therapy treatments in clinical trials is for LCA. CRISPR-Cas9, a genome editing tool, has been shown to be able to disrupt and/or correct harmful mutations, and deliver functional transgenes²⁹. Because of the promising results from the past 2 years of study, clinical trials will begin in 2017 for patients with LCA³⁰. Overcoming the existing challenges will lead to large gains not only in the molecular mechanisms of RP, but in clinical practice as well. Screening, diagnosis, and treatment of individuals will drastically improve, shaping a better outlook not only for RP, but other inherited retinal diseases as well.

REFERENCES

1. Ferrari, S. et al. Retinitis pigmentosa: genes and disease mechanisms. *Curr Genomics.*, 12(4), 238-249 (2011).
2. Daiger, S. P., Sullivan, L. S., & Bowne, S. J. Genes and mutations causing retinitis pigmentosa. *Clin Genet.*, 84(2), 132-141 (2013).
3. Natarajan, S. Retinitis pigmentosa: a brief overview. *Indian J Ophthalmol.*, 59(5), 343-346 (2011).
4. Daiger, S. P., Rossiter, B. J. F., Greenberg, J., Christoffels, A., & Hide, W. Data services and software for identifying genes and mutations causing retinal degeneration. *Invest. Ophthalmol. Vis. Sci.*, 39, S295 (1998).
5. Hartong, D. T., Berson, E. L., & Dryja, T. P. Retinitis pigmentosa. *Lancet*, 368(9549), 1795-1809 (2006).
6. Leroy, B. P & Dharmaraj, S. Leber congenital amaurosis. *Orphanet Encycloped.*, 11, 1-5 (2003).
7. Concepcion, F., & Chen, J. Q344ter mutation causes mislocalization of rhodopsin molecules that are catalytically active: a mouse model of Q344ter-induced retinal degeneration. *PLoS ONE*, 5(6), e10904 (2010).
8. Ali, R. et al. Restoration of photoreceptor ultrastructure and function in retinal degeneration slow mice by gene therapy. *Nature Genetics*, 25(3), 306-310 (2000).
9. Liu, Q., Zuo, J., & Pierce, E. A. The retinitis pigmentosa 1 protein is a photoreceptor microtubule-associated protein. *J Neurosci.*, 24(29), 6427-6436 (2004).
10. Yamashita T. et al. Essential and synergistic roles of RP1 and RP1L1 in rod photoreceptor axoneme and retinitis pigmentosa. *J Neurosci.*, 29(31), 9748-9760 (2009).
11. Crouch, R. K. The visual cycle: generation of 11-*cis* retinal for photoreceptors. <http://www.photobiology.info/Crouch.html> (2009).
12. Cai, X., Conley, S. M., & Naash, M. I. RPE65: role in the visual cycle, human retinal disease and gene therapy. *Ophthalmic Genet.*, 30(2), 57-62 (2009).
13. Duda, T. et al. Mutations in the rod outer segment membrane guanylate cyclase in cone-rod dystrophy cause defects in calcium signaling. *Biochemistry*, 38(42), 13912-13919 (1999).
14. Toriello, H. V. & Franco, B. Oral-Facial-Digital Syndrome Type I. *GeneReviews*. <http://www.ncbi.nlm.nih.gov/books/NBK1188/> (2002).
15. He, S. et al. Retinitis pigmentosa GTPase regulator (RPGR) protein isoforms in mammalian retina: insights into x-linked retinitis pigmentosa and associated ciliopathies. *Vision Res.*, 48(3), 366-376 (2008).
16. Ferreira, P. A. Insights into x-linked retinitis pigmentosa type 3, allied diseases and underlying pathomechanisms. *Hum Mol Genet.*, 14, R259-R267 (2005).
17. Soroush, N., Wunderlich, K., Bauss, K., Nagel-Wolfrum, K., & Wolfrum, U. Usher syndrome protein network functions in the retina and their relation to other retinal ciliopathies. *Adv Exp Med Biol.*, 801, 527-533 (2014).
18. Forsythe, E. & Beales, P. Bardet-biedl syndrome. *Eur J Hum Genet.*, 21, 8-13 (2013).

19. Shin, S. J. et al. Identification of compound heterozygous mutations in the *BBS7* gene in a Korean family with bardet-biedl syndrome. *Ann Lab Med.*, 35(1), 181-184 (2015).
20. Norris, D. P. & Grimes, D. T. Mouse models of ciliopathies: the state of the art. *Dis Model Mech.*, 5(3), 299-312 (2012).
21. M'hamdi, O., Ouertani, I., & Chaabouni-Bouhamed, H. Update on the genetics of bardet-biedl syndrome. *Mol Syndromol.* 5(2), 51-56 (2014).
22. Garcia-Garcia, G. et al. Novel deletions involving the *USH2A* gene in patients with usher syndrome and retinitis pigmentosa. *Mol Vis.*, 20, 1398-1410 (2014).
23. Gibbs, D., Diemer, T., Khanobdee, K., Hu, J., Bok, D., & Williams, D. Function of *MYO7A* in the human RPE and the validity of shaker1 mice as a model for usher syndrome 1B. *Invest Ophthalmol Vis Sci.*, 51(2), 1130-1135 (2010).
24. Rong W. et al. Novel and recurrent *MYO7A* mutations in usher syndrome type 1 and type 2. *PLoS ONE*, 9(5), e97808 (2014).
25. Lopes, V. S. et al. The usher 1B protein, *MYO7A*, is required for normal localization and function of the visual retinoid cycle enzyme, RPE65. *Hum. Mol. Genet.*, 20(13), 2560-2570 (2011).
26. Keats, B. J. & Lentz, J. Usher syndrome type II. *GeneReviews*. <http://www.ncbi.nlm.nih.gov/books/NBK1341/> (1999).
27. Millán, J. M. et al. An update on the genetics of usher syndrome. *Journal of Ophthalmology*, 2011, 8 pages (2011).
28. Williams, D. Usher syndrome: Animal models, retinal function of Usher proteins, and prospects for gene therapy. *Vision Res.*, 48(3), 433-441 (2008).
29. Jang, Y. Y., Cai, L., & Ye, Z. Genome editing systems in novel therapies. *Discov Med.*, 21(113), 57-64 (2016).
30. Han, A.P. Look for CRISPR/Cas9 to treat eye disease first, scientists say. <https://www.genomeweb.com/gene-silencinggene-editing/look-crisprcas9-treat-eye-diseases-first-scientists-say> (2016).