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Genes and mutations causing retinitis pigmentosa

SP Daiger, **LS Sullivan**, and **SJ Bowne**
Human Genetics Center, School of Public Health, The University of Texas Health Science Center, Houston, TX, USA

Abstract

Retinitis pigmentosa (RP) is a heterogeneous set of inherited retinopathies with many disease-causing genes, many known mutations, and highly varied clinical consequences. Progress in finding treatments is dependent on determining the genes and mutations causing these diseases, which includes both gene discovery and mutation screening in affected individuals and families. Despite the complexity, substantial progress has been made in finding RP genes and mutations. Depending on the type of RP, and the technology used, it is possible to detect mutations in 30–80% of cases. One of the most powerful approaches to genetic testing is high-throughput 'deep sequencing', that is, next-generation sequencing (NGS). NGS has identified several novel RP genes but a substantial fraction of previously unsolved cases have mutations in genes that are known causes of retinal disease but not necessarily RP. Apparent discrepancy between the molecular defect and clinical findings may warrant reevaluation of patients and families. In this review, we summarize the current approaches to gene discovery and mutation detection for RP, and indicate pitfalls and unsolved problems. Similar considerations apply to other forms of inherited retinal disease.

Keywords

genetic screening; inherited retinal diseases; next-generation sequencing; phenotype; genotype reconciliation; retinitis pigmentosa; targeted-capture sequencing

Inherited retinal diseases affect more than 200,000 Americans and millions of individuals worldwide (1-3). Dozens of different types of disease are included in this set of diseases, and more than 190 genes have been identified as the cause of one or another form of inherited retinal disease (4, 5). Retinitis pigmentosa (RP) accounts for approximately one-half of cases. RP itself is highly heterogeneous: mutations in more than 50 genes are known to cause non-syndromic RP and nearly 3100 mutations have been reported in these genes (5, 6). Syndromic forms of RP are equally heterogeneous: mutations in 12 genes cause Usher syndrome and 17 genes are associated with Bardet-Biedl syndrome; together these two diseases account for another 1200 pathogenic mutations. In addition to genetic and mutational heterogeneity, different diseases may be caused by mutations in the same gene, symptoms of different diseases may overlap, and there is extensive variation in clinical expression even among individuals sharing the same mutation in the same gene.

Corresponding author: Stephen P.Daiger, PhD, Human Genetics Center, School of Public Health, The University of Texas Health Science Center, 1200 Herman Pressler Drive, Houston, TX 77030, USA. Tel.: +1 713 500 9829; fax: +1 713 500 0900; stephen.p.daiger@uth.tmc.edu.

Conflict of interest
The authors declare no conflict of interest.

Despite the complexity, significant progress has been made in recent years in identifying novel RP genes and in screening patients for pathogenic mutations. This is partly the result of development of high-throughput mapping and sequencing techniques, but is also testimony to the large number of investigators and research groups working in this area. In the past two decades, the number of research groups in the world focused on RP genetics has gone from a handful to dozens. The potential options for treatments have also increased markedly. The purpose of this review is to provide an overview of the current status of RP genes. References are largely chosen for illustration; a more comprehensive list is found in RetNet, http://www.sph.uth.tmc/edu/retnet (5). Inherited retinopathies as a broad class of diseases are reviewed in other publications (4, 7). This is a fast-moving field and it is encouraging to note that any review will be out of date sooner rather than later.

Heterogeneity

Retinitis pigmentosa is a progressive, degenerative disease of the retina leading to profound loss of vision or blindness (3). The clinical hallmarks of RP are night blindness, often starting in adolescence, followed by progressive loss of peripheral vision and subsequent loss of central vision. By midlife, RP patients may retain a few degrees of central vision but in many cases the disease culminates in complete blindness. Findings on retinal examination include ‘bone spicule’ pigmentary deposits, retinal vessel attenuation, and characteristic changes in electroretinogram (ERG) patterns. At a cellular level, a simplified view of RP is progressive dysfunction and loss of rod photoreceptors, first affecting night vision in the rod-rich mid-peripheral retina, then progressing into the cone-rich central retina, with eventual loss of cones either as a direct result of the disease process or secondary to the death of rods.

Within this broad picture, though, there is considerable variation in age of onset, rate of progression, rod *vs* cone involvement, involvement of other retinal cells such as RPE, secondary symptoms such as cystic macular edema, and many other features. RP which is present at birth or soon after is often referred to as Leber congenital amaurosis (LCA). RP may occur alone, as non-syndromic RP, without other clinical findings, or as syndromic or systemic RP with other neurosensory disorders, developmental abnormalities, or complex clinical phenotypes. Usher syndrome is RP with congenital or early onset deafness. Bardet-Biedl syndrome (BBS) is RP with kidney disease, obesity, polydactyly and developmental delay. RP may also be secondary to systemic disorders such as mitochondrial diseases or various forms of degenerative cerebellar disease. For simplicity, this review is limited to non-syndromic RP, Usher syndrome and BBS (for one reason, because the diseases overlap). Other syndromic and systemic forms of RP are listed in RetNet (5).

Retinitis pigmentosa is exceptionally heterogeneous. This includes (i) *genetic heterogeneity* – many different genes may cause the same disease phenotype; (ii) *allelic heterogeneity* – there may be many different disease-causing mutations in each gene; (iii) *phenotypic heterogeneity* – different mutations in the same gene may cause different diseases; and (iv) *clinical heterogeneity* – the same mutation in different individuals may produce different clinical consequences, even among members of the same family. The extent of heterogeneity of RP can be confusing to patients and clinicians alike, and is a confounding factor in diagnosis.

The most obvious complications are genetic and allelic. Currently, mutations in 56 genes are known to cause non-syndromic RP (Table 1). Twelve genes account for Usher syndrome and 17 account for BBS (Tables 2 and 3). If genes for LCA and for other syndromic or systemic forms of RP are included, at least 100 ‘RP-related’ genes are known. Allelic or mutational heterogeneity is equally striking. Counting all the genes known to cause non-

syndromic RP, nearly 3100 disease-causing mutations are reported in mutation databases (Table 1). Discounting over-laps with non-syndromic RP, genes causing Usher syndrome and BBS account for at least another 1200 mutations (Tables 2 and 3).

Although some of the publically reported mutations may, later, turn out to be non-pathogenic, this is still a significant underestimate because many novel mutations are listed in private databases and are not yet in the public domain. Among other concerns, there is need for more systematic collection of mutation phenotype–genotype information for inherited retinal diseases, a need addressed, for example, by the Leiden Open Variation Database (8).

Equally confusing is the overlap between disease types, disease names, and clinical consequences. First, different mutations in the same gene may cause distinctly different conditions. For example, even though most rhodopsin mutations cause autosomal-dominant RP and most RPE65 mutations cause recessive LCA, some rhodopsin mutations may be recessive acting and some RPE65 mutations may be dominant acting (9-13). Usher syndrome mutations are recessive and cause both deafness and RP, but mutations in two Usher genes, CLRN1 and USH2A, may cause recessive RP only (14, 15).

For non-syndromic RP, mutations in 23 genes are known to cause autosomal-dominant RP, 36 genes cause recessive RP, and 3 genes cause X-linked RP (5). However, Table 1 shows that several of these diseases overlap with each other and Tables 1–3 show that many genes cause multiple diseases. In some cases the ‘secondary’ disease is rare (e.g. recessive rhodopsin or dominant RPE65 mutations), but in some cases it is common (e.g. recessive RP and USH2A). Generally, there is no simple mapping between gene and disease in most cases.

Finally, even identical mutations within the same gene may produce different clinical findings. Variation between individuals in age of onset or rate of progression is not unexpected, but, for example, mutations in PRPF31 are non-penetrant in some family members, (16, 17) and mutations in PRPH2 (RDS) produce a wide range of macular, peripheral or pan-retinal symptoms (18, 19). One consequence is that members of the same family, seen by different clinicians, may have diagnoses that are consistent with findings in the individual but inconsistent with the family. Overall, there is considerable overlap between diseases caused by RP genes even though different names are given to specific types of disease. This is well illustrated by the over-lapping disease nomenclature proposed by Berger et al. for inherited retinal diseases (4).

Fortunately, molecular techniques allow identification of the underlying gene and mutation or mutations in many cases, adding a molecular diagnosis to the clinical diagnosis. Nevertheless, in some cases this leads to apparent contradictions that require further analysis to resolve.

Technical approaches

The standard techniques for gene discovery and mutation detection – linkage mapping and DNA sequencing – have been used for many years. However, development of high-density and high-throughput techniques in the past 10 years has increased the power of these methods by orders of magnitude.

For linkage mapping, high-density SNP (single-nucleotide polymorphism) arrays, such as the AFFYMETRIX 6.0 SNP/CNV array, (20) allow linkage testing against nearly 1 million genetic markers. For practical purposes, these are often collapsed to around 10,000 most-informative markers, with known relationships to contiguous markers. However, even with

smaller marker sets, there is a serious issue of the large number of independent tests (multiple comparisons) leading to apparent linkage 'hits' by chance alone. Fortunately, there are many more, highly-variable genetic markers in the human genome that can be used to refine linkage mapping (9). Several RP genes have first been localized by linkage mapping in recent years (21-25).

One consequence of availability of dense SNP marker sets is that it is possible to identify regions on homologous chromosomes that are identical-by-descent, that is, regions on a matching pair of chromosomes that derive from a single chromosome in a relatively recent ancestor. This identifies the chromosomal location of identical recessive mutations in families with consanguinity or recent within-family matings. This approach to mapping recessive genes is called homozygosity mapping or autozygosity mapping (26). It has been very productive in identifying RP genes in inbred families and in ethnic populations where inbreeding is common (27-31). Surprisingly, even in families without evidence of consanguinity, recessive RP mutations are more often identical-by-descent than expected, thus expanding the utility of homozygosity mapping (26).

Methods for detecting mutations at a DNA sequence level include Sanger sequencing, still called the gold standard of sequencing, array-based detection of specific mutations (e.g. APEX, 'array-primer extension' (32-34)), ultra-high-throughput sequencing and others. Of these, the major advance in recent years in finding RP genes is application of ultra-high-throughput sequencing, generally referred to as next-generation sequencing (NGS) (35). Conventional Sanger sequencing is usually done using semiautomated, multilane capillary electrophoresis (itself a major improvement over earlier methods). In contrast, NGS does millions of sequencing runs in parallel on micron-sized beads or in comparable micro-wells, completing up to a billion base-pair reads per run. That is, NGS sequencing is at least 1000 times faster than conventional sequencing, and much less expensive per sequence.

There are several NGS methods and numerous distinct applications (36, 37). What most methods have in common is short-read, shot-gun sequencing: DNA is first fragmented into short sequences, read lengths are in the range of 100 to 200 base pairs, and computational methods are used to 'reassemble' the short reads into larger constructs. This allows highly accurate, extremely rapid sequencing of large regions of the human genome, but certain features of human DNA, such as deletions and rearrangements, expanded repeats, and haplotypes, are not accessible to NGS without additional steps. Also, because of the sheer volume of data produced by NGS, dedicated bioinformatic resources are required to fully utilize the results.

Despite these limitations, NGS has been exceptionally productive in gene discovery and mutation detection for RP. Broadly, there are three NGS strategies: whole-exome NGS, whole-genome NGS and targeted-capture NGS. Whole-exome NGS involves capture of all protein-coding regions, that is, all exons, constituting about 1.5% of the human genome, followed by NGS. By definition this technique is limited to finding mutations in coding regions only, but nonetheless it has led to identification of several RP genes and novel mutations (9, 38, 39). Whole-genome NGS covers nearly all the human genome (about 98%), and avoids potential artifacts introduced by exon capture, but is not yet in routine use for gene discovery. The principal limitations are sequencing costs, and management and analysis of the resulting massive data sets. However, it is likely that whole-genome sequencing will become routine in the near future, especially with development of 'third generation' technologies (40).

Targeted capture, the third NGS strategy, limits testing to exons of known disease-causing genes (41) – in the case of retinal diseases, for example, testing only the 190-plus genes in

RetNet (5). The disadvantage, of course, is that no new genes can be identified. The advantages are that the analysis 'space' is much smaller, more is known, *a priori*, about each gene, and costs are much lower. Thus this is currently an optimal approach to mutation screening for RP, with many applications (42-47).

Finally, some mutations are not easily detected by conventional sequencing or NGS, particularly large deletions and rearrangements. Some deletions can be detected by SNP arrays, and the Affymetrix 6.0 SNP/CNV arrays includes copy-number probes (CNVs) for deletion detection (20). PCR-amplification based methods, such as MLPA or qPCR, can detect much smaller deletions. This is a significant issue as nearly 3% of cases of autosomal-dominant RP are caused by deletions in PRPF31 not detectable by sequencing (17, 48). Similar deletions and rearrangements are found in ABCA4, a common cause of recessive RP, and in RPGR, the principal cause of X-linked RP (49). However, X-linked deletions are easily detected in hemizygous males, and the principal problem in sequencing RPGR is the repetitive nature of ORF15.

Current status of gene discovery and mutation detection

Identification of novel genes causing inherited retinal diseases, including RP, has progressed at a steady, linear rate for nearly 20 years (Fig. 1). Although the tools for gene discovery are much more powerful, the steady rate in recent years suggests that, in general, each new gene is rarer than preceding genes and thus more difficult to detect. Whole-genome NGS may accelerate gene discovery, but it is possible that the remaining, unknown RP genes are very rare. However, there is no meaningful way to predict the remaining number of RP genes.

The meaningful questions in this context are (i) in what fraction of RP patients can disease-causing mutations be detected today, and (ii) when will it be possible to find mutations in nearly all patients, say, at least 95%? The answer to the first question depends on the technology used and the type of RP. Combining results from conventional Sanger sequencing and targeted-capture NGS, using rough estimates, it is possible to detect the underlying pathogenic mutation or mutations in 20–30% of autosomal recessive RP cases, 60–70% of autosomal-dominant cases, 80–85% of X-linked cases, and more than 85% of Usher and BBS cases (44, 50) [and S.P. Daiger, unpublished data].

Simplex (isolated) RP cases are more complicated. Traditionally, simplex RP cases are predicted to be recessive, with unaffected carrier parents. This is true in many cases, but there are exceptions. At least 15% of males with RP and no other affected family members have mutations in the X-linked genes RPGR or RP2 (51). *De novo* autosomal-dominant mutations account for at least 1–2% of simplex cases (45, 52). Targeted NGS identifies mutations in 19–36% of simplex RP cases, but confirming pathogenicity in these cases is problematic (44-47). A further complication is that the carrier frequency for all inherited retinal disease mutations in unaffected individuals may exceed 20% (53). That is, each mutation is extremely rare, but there are so many genes and so many mutations, that in aggregate they are common.

Prediction is risky, but given rapid advances in DNA sequencing methods, and continued identification of new RP genes, it is reasonable to expect that within 5 years it will be possible to detect the disease-causing gene and mutation or mutations in 95% of patients. This is assuming that most of the remaining cases are monogenic, that is, caused by a single gene in each individual. Since digenic forms of RP and triallelic forms of BBS are already known, polygenic inheritance of retinal diseases cannot be discounted (54, 55).

Finally, genetic diagnosis of RP may change the family diagnosis or raise questions about the relationship between genotype and phenotype. For example, at least 8% of families with

a provisional diagnosis of autosomal-dominant RP actually have mutations in X-linked RP genes (56). Mutations in genes commonly associated with Usher syndrome or BBS may cause non-syndromic RP (14, 15, 57). Other examples arise from targeted-capture NGS. This can be confusing for the patient and requires thoughtful explanation and counseling. In some cases, it may require redefining the family's disease. Reconciling the clinical phenotype, family history and genetic findings is a critical, new step in the diagnosis of inherited retinal diseases.

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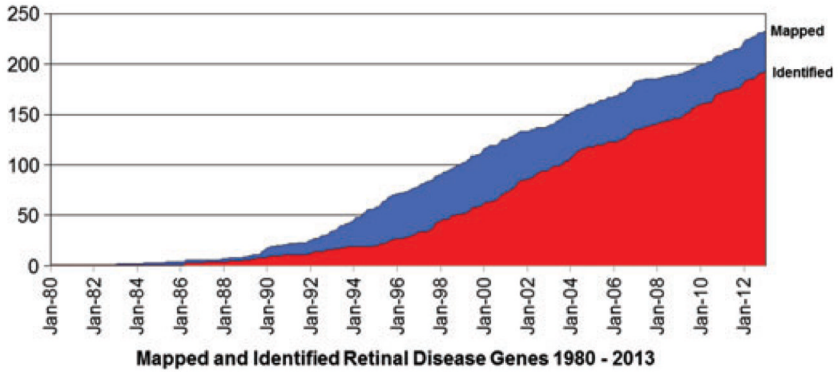

Fig. 1.
Mapped and identified retinal disease genes over three decades.

Table 1

Genes causing non-syndromic retinitis pigmentosa[a]

	Symbol	Location	Protein	Type of retinitis pigmentosa	Other diseases	Mutations
1	ABCA4	1p22.1	ATP-binding cassette transporter – retinal	Autosomal recessive	Recessive macular dystrophy; recessive fundus flavimaculatus; recessive cone-rod dystrophy	680
2	BEST1	11q12.3	Bestrophin 1	Autosomal dominant; autosomal recessive	Dominant vitreo-retinochoroidopathy; recessive bestrophinopathy; dominant Best type macular dystrophy	232
3	C2ORF71	2p23.2	Chromosome 2 open reading frame 71	Autosomal recessive		13
4	C8ORF37	8q22.1	Chromosome 8 open reading frame 37	Autosomal recessive	Recessive cone-rod dystrophy	4
5	CA4	17q23.2	Carbonic anhydrase IV	Autosomal dominant		6
6	CERKL	2q31.3	Ceramide kinase-like protein	Autosomal recessive	Recessive cone-rod dystrophy with inner retinopathy	8
7	CLRN1	3q25.1	Clarin-1	Autosomal recessive	Recessive Usher syndrome	23
8	CNGA1	4p12	Rod cGMP-gated channel alpha subunit	Autosomal recessive		8
9	CNGB1	16q13	Rod cGMP-gated channel beta subunit	Autosomal recessive		6
23	CRB1	1q31.3	Crumbs homolog 1	Autosomal recessive	Recessive Leber congenital amaurosis; dominant pigmented paravenous chorioretinal atrophy	183
11	CRX	19q13.32	Cone-rod otx-like photoreceptor homeobox transcription factor	Autosomal dominant	Recessive, dominant and de novo Leber congenital amaurosis; dominant cone-rod dystrophy	51
12	DHDDS	1p36.11	Dehydrodolichyl diphosphate synthetase	Autosomal recessive		1
13	EYS	6q12	Eyes shut/spacemaker (*Drosophila*) homolog	Autosomal recessive		118
14	FAM161A	2p15	Family with sequence similarity 161 member A	Autosomal recessive		6
15	FSCN2	17q25.3	Retinal fascin homolog 2, actin bundling protein	Autosomal dominant	Dominant macular dystrophy	1
16	GUCA1B	6p21.1	Guanylate cyclase activating protein 1B	Autosomal dominant	Dominant macular dystrophy	3
17	IDH3B	20p13	NAD(+)-specific isocitrate dehydrogenase 3 beta	Autosomal recessive		2
18	IMPDH1	7q32.1	Inosine monophosphate dehydrogenase 1	Autosomal dominant	Dominant Leber congenital amaurosis	14
19	IMPG2	3q12.3	Interphotoreceptor matrix proteoglycan 2	Autosomal recessive		10

	Symbol	Location	Protein	Type of retinitis pigmentosa	Other diseases	Mutations
20	KLHL7	7p15.3	Kelch-like 7 protein (*Drosophila*)	Autosomal dominant		3
21	LRAT	4q32.1	Lecithin retinol acyltransferase	Autosomal recessive	Recessive Leber congenital amaurosis	10
22	MAK	6p24.2	Male germ-cell associated kinase	Autosomal recessive		9
23	MERTK	2q13	c-mer protooncogene receptor tyrosine kinase	Autosomal recessive		27
24	NR2E3	15q23	Nuclear receptor subfamily 2 group E3	Autosomal dominant; autosomal recessive	Recessive Stargardt disease; Goldmann-Favre syndrome; recessive enhanced S-cone syndrome	45
25	NRL	14q11.2	Neural retina lucine zipper	Autosomal dominant; autosomal recessive	Recessive retinitis pigmentosa	14
26	OFD1	Xp22.2	Oral-facial-digital syndrome 1 protein	X-linked	Orofaciodigital syndrome 1, Simpson-Golabi-Behmel syndrome 2	127
27	PDE6A	5q33.1	cGMP phosphodiesterase alpha subunit	Autosomal recessive		16
28	PDE6B	4p16.3	Rod cGMP phosphodiesterase beta subunit	Autosomal recessive	Dominant congenital stationary night blindness	39
29	PDE6G	17q25.3	Phosphodiesterase 6G cGMP-specific rod gamma	Autosomal recessive		1
30	PRCD	17q25.1	Progressive rod-cone degeneration protein	Autosomal recessive		2
31	PROM1	4p15.32	Prominin 1	Autosomal recessive	Dominant Stargardt-like and bulls eye macular dystrophy; dominant cone-rod dystrophy	9
32	PRPF3	1q21.2	Human homolog of yeast pre-mRNA splicing factor 3	Autosomal dominant		3
33	PRPF6	20q13.33	Human homolog of yeast pre-mRNA splicing factor 6	Autosomal dominant		2
34	PRPF8	17p13.3	Human homolog of yeast pre-mRNA splicing factor C8	Autosomal dominant		21
35	PRPF31	19q13.42	Human homolog of yeast pre-mRNA splicing factor 31	Autosomal dominant		65
36	PRPH2	6p21.1	Peripherin 2	Autosomal dominant; digenic with ROM1	Dominant macular dystrophy; dominant vitelliform MD; dominant cone-rod dystrophy; dominant central areolar choroidal dystrophy	123
37	RBP3	10q11.22	Retinol binding protein 3, interstitial	Autosomal recessive		2

	Symbol	Location	Protein	Type of retinitis pigmentosa	Other diseases	Mutations
38	RDH12	14q24.1	Retinol dehydrogenase 12	Autosomal dominant; autosomal recessive	Recessive Leber congenital amaurosis	66
39	RGR	10q23.1	RPE-retinal G protein-coupled receptor	Autosomal recessive	Dominant choroidal sclerosis	7
40	RHO	3q22.1	Rhodopsin	Autosomal dominant; autosomal recessive	Dominant congenital stationary night blindness	161
41	RLBP1	15q26.1	Retinaldehyde-binding protein 1	Autosomal recessive	Recessive Bothnia dystrophy; recessive retinitis punctata albescens; recessive Newfoundland rod-cone dystrophy	20
42	ROM1	11q12.3	Retinal outer segment membrane protein 1	Autosomal dominant; digenic w/ PRPH2		11
43	RP1	8q12.1	RP1 protein	Autosomal dominant; autosomal recessive	Autosomal dominant and recessive	67
44	RP2	Xp11.23	Retinitis pigmentosa 2 (X-linked)	X-linked		76
45	RP9	7p14.3	RP9 protein or PIM1-kinase associated protein 1	Autosomal dominant		2
46	RPE65	1p31.2	Retinal pigment epithelium-specific 65 kDa protein	Autosomal dominant; autosomal recessive	Recessive Leber congenital amaurosis	134
47	RPGR	Xp11.4	Retinitis pigmentosa GTPase regulator	X-linked	X-linked cone dystrophy 1; X-linked atrophic macular dystrophy	151
48	SAG	2q37.1	Arrestin (s-antigen)	Autosomal recessive	Recessive Oguchi disease	11
49	SEMA4A	1q22	Semaphorin 4A	Autosomal dominant	Dominant cone-rod dystrophy	3
50	SNRNP200	2q11.2	Small nuclear ribonucleoprotein 200 kDa (U5)	Autosomal dominant		7
51	SPATA7	14q31.3	Spermatogenesis associated protein 7	Autosomal recessive	Recessive Leber congenital amaurosis	15
52	TOPORS	9p21.1	Topoisomerase I binding arginine/serine rich protein	Autosomal dominant		8
53	TTC8	14q32.11	Tetratricopeptide repeat domain 8	Autosomal recessive	Recessive Bardet-Biedl syndrome	14
54	TULP1	6p21.31	Tubby-like protein 1	Autosomal recessive	Recessive Leber congenital amaurosis	31
55	USH2A	1q41	Usherin	Autosomal recessive	Recessive Usher syndrome	392
56	ZNF513	2p23.3	Zinc finger protein 513	Autosomal recessive		1
					Total	**3064**

[a]Tables are based on the RetNet database, http://www.sph.uth.tmc.edu/retnet/, accessed May 2013 (5), and the Human Gene Mutation Database, http://www.hgmd.cf.ac.uk/, accessed May 2013 (6). References are in RetNet. Some genes appear in more than one table so the sum total of distinct genes in the tables, 82, is less than the sum of the three tables together.

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Table 2

Genes causing Usher syndrome[a]

	Symbol	Location	Protein	Type of Usher syndrome	Other diseases	Mutations
1	ABHD12	2p11.21	Abhydrolase domain containing protein 12	Autosomal recessive type 3-like	Recessive PHARC syndrome type	5
2	CDH23	10q22.1	Cadherin-like gene 23	Autosomal recessive 1d; digenic with PCDH15	Recessive deafness without retinitis pigmentosa	167
3	CIB2	15q25.1	Calcium and integrin binding family member 2	Autosomal recessive type 1J		7
4	CLRN1	3q25.1	Clarin-1	Autosomal recessive type 3	Recessive retinitis pigmentosa	see RP
5	DFNB31	9q32	Whirlin	Autosomal recessive type 2	Recessive deafness without retinitis pigmentosa	13
6	GPR98	5q14.3	Monogenic audiogenic seizure susceptibility 1 homolog	Autosomal recessive type 2	Dominant/recessive febrile convulsions	54
7	HARS	5q31.3	Histidyl-tRNA synthetase	Autosomal recessive	Recessive HARS syndrome	2
8	MYO7A	11q13.5	myosin VIIA	Recessive type 1b; recessive USH3-like	Recessive deafness without retinitis pigmentosa	263
9	PCDH15	10q21.1	Protocadherin 15	Autosomal recessive type 1f; digenic with CDH23	Recessive deafness without retinitis pigmentosa	52
10	USH1C	11p15.1	harmonin	Autosomal recessive Acadian	Recessive deafness without retinitis pigmentosa; recessive RP with late-onset hearing loss	26
11	USH1G	17q25.1	Human homolog of mouse scaffold protein containing ankyrin repeats and SAM domain	Autosomal recessive Usher syndrome		11
12	USH2A	1q41	Usherin	Autosomal recessive type 2a	Recessive retinitis pigmentosa	see RP
					Total	**600**

RP, retinitis pigmentosa.

[a]Tables are based on the RetNet database, http://www.sph.uth.tmc.edu/retnet/, accessed May 2013 (5), and the Human Gene Mutation Database, http://www.hgmd.cf.ac.uk/, accessed May 2013 (6). References are in RetNet. Some genes appear in more than one table so the sum total of distinct genes in the tables, 82, is less than the sum of the three tables together.

Table 3

Genes causing Bardet-Biedl syndrome (BBS)[a]

	Symbol	Location	Protein	Type of BBS	Other diseases	Mutations
1	ARL6	3q11.2	ADP-ribosylation factor-like 6	Autosomal recessive		14
2	BBS1	11q13	BBS1 protein	Autosomal recessive		65
3	BBS2	16q12.2	BBS2 protein	Autosomal recessive		61
4	BBS4	15q24.1	BBS4 protein	Autosomal recessive		29
5	BBS5	2q31.1	Flagellar apparatus-basal body protein DKFZp7621194	Autosomal recessive		18
6	BBS7	4q27	BBS7 protein	Autosomal recessive		26
7	BBS9	7p14.3	Parathyroid hormone-responsive B1 protein	Autosomal recessive		27
8	BBS10	12q21.2	BBS10 (C12orf58) chaperonin	Autosomal recessive		76
9	BBS12	4q27	BBS12 protein	Autosomal recessive		45
10	CEP290	12q21.32	Centrosomal protein 290 kDa	Autosomal recessive	Recessive Joubert syndrome; recessive Leber congenital amaurosis; recessive Meckel syndrome; recessive Senior-Loken syndrome	157
11	INPP5E	9q34.3	Inositol polyphosphate-5-phosphatase E	Autosomal recessive	Recessive MORM syndrome; recessive Joubert syndrome	7
12	LZTFL1	3p21.31	Leucine zipper transcription factor-like 1	Autosomal recessive		1
13	MKKS	20p12.2	McKusick-Kaufman syndrome protein	Autosomal recessive		44
14	MKS1	17q22	Meckel syndrome type 1 protein	Autosomal recessive	Recessive Meckel syndrome	26
15	SDCCAG8	1q43	Serologically defined colon cancer antigen 8	Autosomal recessive	Recessive ciliopathy-related nephronophthisis,	13
16	TRIM32	9q33.1	Tripartite motif-containing protein 32	Autosomal recessive	Recessive limb-girdle muscular dystrophy	8
17	TTC8	14q32.11	Tetratricopeptide repeat domain 8	Autosomal recessive	Recessive retinitis pigmentosa	see RP
					Total	**617**

RP, retinitis pigmentosa.

[a]Tables are based on the RetNet database, http://www.sph.uth.tmc.edu/retnet/, accessed May 2013 (5), and the Human Gene Mutation Database, http://www.hgmd.cf.ac.uk/, accessed May 2013 (6). References are in RetNet. Some genes appear in more than one table so the sum total of distinct genes in the tables, 82, is less than the sum of the three tables together.