



Genes and Mutations Causing Autosomal Dominant Retinitis Pigmentosa

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Retinitis pigmentosa (RP) has a prevalence of approximately one in 4000; 25%–30% of these cases are autosomal dominant retinitis pigmentosa (adRP). Like other forms of inherited retinal disease, adRP is exceptionally heterogeneous. Mutations in more than 25 genes are known to cause adRP, more than 1000 mutations have been reported in these genes, clinical findings are highly variable, and there is considerable overlap with other types of inherited disease. Currently, it is possible to detect disease-causing mutations in 50%–75% of adRP families in select populations. Genetic diagnosis of adRP has advantages over other forms of RP because segregation of disease in families is a useful tool for identifying and confirming potentially pathogenic variants, but there are disadvantages too. In addition to identifying the cause of disease in the remaining 25% of adRP families, a central challenge is reconciling clinical diagnosis, family history, and molecular findings in patients and families.

Retinitis pigmentosa (RP) is an inherited dystrophic or degenerative disease of the retina with a prevalence of roughly one in 4000 (Haim 2002; Daiger et al. 2007). Typically, the disease progresses from the midperiphery of the retina into the central retina and, in many cases, into the macula and fovea (Heckenlively and Daiger 2007; Fahim et al. 2013). Clinical features include night blindness starting in adolescence, followed by progressive loss of peripheral vision—referred to as “tunnel vision”—culminating in legal blindness or complete blindness in adulthood. Characteristic retinal findings on examination include bone-spicule formations and attenuated blood vessels, reduced visual fields, reduced and/or abnormal electroretino-

grams (ERGs), changes in structure imaged by optical coherence tomography (OCT), and subjective changes in visual function (Fishman et al. 2005). However, features and findings are highly variable among patients, even among patients within the same family.

RP is exceptionally heterogeneous at a genetic level. All modes of inheritance are encountered: dominant, recessive, autosomal, X-linked, and even mitochondrial (Berger et al. 2010). It is assumed that each patient has a monogenic form of disease (or digenic in rare cases) but many different genes account for disease in RP patients as a group. Currently, mutations in more than 66 genes are known to cause nonsyndromic RP and an additional 31 genes cause

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syndromic forms such as Usher syndrome and Bardet–Biedl syndrome (Daiger et al. 2013; RetNet 2014). There are also many disease-causing mutations reported in these genes. More than 3100 mutations are listed in the Human Gene Mutation Database (HGMD) (HGMD 2014) in nonsyndromic RP genes alone (Daiger et al. 2013).

This review focuses on nonsyndromic autosomal dominant retinitis pigmentosa (adRP). This is partly to simplify the discussion but also because finding genes and mutations causing adRP entails unique opportunities and pitfalls. In addition, our laboratory has worked with adRP families for the past 25 years affording us insights into these issues. Despite the limited focus, many observations regarding genes and mutations causing adRP apply equally well to other forms of inherited retinopathy.

FINDING GENES AND MUTATIONS CAUSING adRP

The successes in finding adRP genes and disease-causing mutations over the past two decades are striking. Table 1 lists genes in which mutations are reported to cause adRP. References are in RetNet (RetNet 2014, see <https://sph.uth.edu/retnet/>). There are currently 25 reported adRP genes and an additional linked gene, RP63, which maps to human chromosome 6q23 (Kannabiran et al. 2012). The HGMD database (HGMD 2014) lists more than 1000 mutations in these genes, although not all are dominant-acting (and not all are pathogenic). To date, mutations in the known adRP genes account for 50%–75% of cases, depending on the tests performed and populations screened. Nonetheless, significant problems remain.

For example, it should be easy to name genes known to cause adRP, but it is not. In recent years, the simple idea that one gene leads to one disease has proven highly inaccurate, especially for inherited retinal diseases. A gene first identified as the cause of one form of disease, for example, recessive RP, may harbor mutations that cause another form of retinal disease or mutations with a different mode of inheritance for example, adRP. Table 1 lists alternate forms

of disease associated with adRP genes. One consequence of this overlap is that any simple count of “RP genes” is often arbitrary.

Likewise, there are complications in detecting disease-causing mutations in adRP genes. For one, the initial diagnosis in a family may be misleading. That is, because of exceptional clinical variation, affected family members may have different clinical diagnoses, or the mode of inheritance may be misconstrued. For example, families with X-linked RP and affected carrier females may be mistaken as adRP (Churchill et al. 2013). Further, a significant fraction of RP patients present as isolated cases, with no known affected relatives, so the mode of inheritance is undetermined. Also, because different mutations in the same gene can produce different clinical consequences, the actual mutation may be in a known gene not commonly associated with adRP. Examples include rare adRP mutations in RPE65 (Bowne et al. 2011a) and RDH12 (Fingert et al. 2008), genes more likely to cause recessive RP or recessive Leber congenital amaurosis, respectively.

Beyond these complications, there is the general problem of variants of unknown significance (VUS), that is, rare, potentially pathogenic variants in known adRP genes for which the evidence is equivocal. This is a fundamental problem in medical genetics given the extensive background of rare and apparently damaging variants in the human population (Marth et al. 2011). Suggestions for scoring potentially pathogenic variants are discussed in the next section.

Finally, there are substantial difficulties in identifying novel adRP genes. Three advanced technologies using next-generation sequencing (NGS) are in use: targeted retinal-gene capture NGS (Simpson et al. 2011; Audo et al. 2012; Neveling et al. 2012; O’Sullivan et al. 2012; Chen et al. 2013; Eisenberger et al. 2013; Glockle et al. 2013; Wang et al. 2014), whole-exome NGS (Bowne et al. 2011a; Ozgul et al. 2011; Tucker et al. 2011; Zeitz et al. 2013; El Shamieh et al. 2014; Jin et al. 2014; Sergouniotis et al. 2014), and whole-genome NGS (Nishiguchi et al. 2013). Each has advantages and disadvantages.

Because targeted retinal-capture NGS examines only a small portion of the human

Table 1. Genes reported to cause autosomal dominant retinitis pigmentosa pigmentosa (in chromosomal order)

	Symbol	Gene/protein	Chromosome	Alternate diseases	Function
1	RPE65	Retinal pigment epithelium-specific 65 kD protein	1p31.2	Recessive retinitis pigmentosa; recessive Leber congenital amaurosis	Visual cycle
2	PRPF3	Pre-mRNA processing factor 3	1q21.2		RNA processing
3	SEMA4A	Semaphorin 4A	1q22	Dominant cone-rod dystrophy	Neuronal or immune response
4	SNRNP200	Small nuclear ribonucleoprotein 200 kDa (U5)	2q11.2		RNA processing
5	RHO	Rhodopsin	3q22.1	Dominant congenital stationary night blindness; recessive retinitis pigmentosa	Phototransduction, outer segment membrane structure
6	GUCA1B	Guanylate cyclase activating protein 1B	6p21.1	Dominant macular dystrophy	Phototransduction
7	PRPH2	Peripherin 2	6p21.1	Dominant macular dystrophy; digenic retinitis pigmentosa with ROM1; dominant adult vitelliform macular dystrophy; dominant cone-rod dystrophy; dominant central areolar choroidal dystrophy	Outer segment membrane structure
8	RP9	RP9 protein or PIM1-kinase associated protein 1	7p14.3		Unknown
9	KLHL7	Kelch-like 7 protein (<i>Drosophila</i>)	7p15.3		Ubiquitination pathway
10	IMPDH1	Inosine monophosphate dehydrogenase 1	7q32.1	Dominant Leber congenital amaurosis	Purine or amino acid synthesis
11	RP1	RP1 protein	8q12.1	Recessive retinitis pigmentosa	Ciliary structure/function
12	TOPORS	Topoisomerase I binding arginine/serine rich protein	9p21.1		Ciliary structure/function
13	PRPF4	Pre-mRNA processing factor 4	9q32		RNA processing
14	HK1	Hexokinase 1	10q22.1		Glucose metabolism
15	BEST1	Bestrophin 1	11q12.3	Dominant vitreoretinopathopathy; recessive bestrophinopathy; recessive retinitis pigmentosa; dominant macular dystrophy, Best type	Visual cycle and chloride channel

Continued

Table 1. *Continued*

	Symbol	Gene/protein	Chromosome	Alternate diseases	Function
16	ROM1	Retinal outer segment membrane protein 1	11q12.3	Digenic retinitis pigmentosa with PRPH2	Outer segment membrane structure
17	NRL	Neural retina luciferase zipper	14q11.2	Recessive retinitis pigmentosa	Transcription factor
18	RDH12	Retinol dehydrogenase 12	14q24.1	Recessive Leber congenital amaurosis with severe childhood retinal dystrophy	Visual cycle
19	NR2E3	Nuclear receptor subfamily 2 group E3	15q23	Recessive retinitis pigmentosa in Portuguese Crypto Jews; recessive Goldmann–Favre syndrome; recessive enhanced S-cone syndrome (ESC); combined dominant and recessive retinopathy	Transcription factor
20	PRPF8	Pre-mRNA processing factor 8	17p13.3		RNA processing
21	CA4	Carbonic anhydrase IV	17q23.2		Retinal capillary structure/function
22	FSCN2	Retinal fascin homolog 2, actin bundling protein	17q25.3	Dominant macular dystrophy	Ciliary structure/function
23	CRX	Cone–rod otx-like photoreceptor homeobox transcription factor	19q13.32	Recessive, dominant and de novo Leber congenital amaurosis; dominant cone–rod dystrophy	Transcription factor
24	PRPF31	Pre-mRNA processing factor 31	19q13.42		RNA processing
25	PRPF6	Pre-mRNA processing factor 6	20q13.33		RNA processing

References as in RetNet, <https://sph.uth.edu/retnet/>, and Sullivan et al. 2014 (HK1).

genome, that is, exons of known retinal genes and candidate genes, analysis of sequence data is simplified. Also, retinal capture panels are optimized for each exon and include retinal-specific splice variants. However, retinal-capture NGS is limited to known genes and detects a large number of VUS mutations (as do all NGS methods). In contrast, whole-exome sequencing is a powerful tool for identifying novel disease-causing genes but perforce is limited to exons, whereas whole genome NGS avoids this limitation but presents a very complex problem in data analysis. For autosomal dominant dis-

eases, the problems are compounded by the need to detect a single, heterozygous mutation in a diploid organism, the proverbial needle-in-a-hay-stack.

Further, because NGS methods are based on short-read, paired-end, and shotgun sequencing, they are underpowered for detecting deletions, insertions, and variable-length repetitive elements. As examples, large deletions in the PRPF31 gene account for 2.5% of adRP cases (Sullivan et al. 2006b), but are generally not detectable by NGS, and the repetitive elements of the ORF15 region of the X-linked RP gene

RPGR are refractory to short-read sequencing (Churchill et al. 2013).

Fortunately, segregation testing and linkage analysis in adRP families address many of these problems. Segregation testing—determining if a putative disease-causing variant tracks with disease in a family—can support or exclude pathogenicity. Complications are the late onset of disease and nonpenetrance. That is, a clinically unaffected family member may carry a disease allele, either because the disease has not manifested yet or because the mutation is nonpenetrant in that individual. An example of the latter is mutations in PRPF31 for which nonpenetrance may be as high as 20% (McGee et al. 1997; Venturini et al. 2012). However, nonpenetrance is not common among other adRP genes. Conversely, absence of a putative mutation in an affected family member is usually strong evidence against pathogenicity.

Linkage analysis tests for cosegregation of polymorphic markers with disease in a family. Loosely, there are two contrasting approaches, linkage exclusion and linkage inclusion. Linkage exclusion is simply exclusion of a known adRP gene by recombination between polymorphic markers within or contiguous to the site. For example, small sets of highly variable STR (short-tandem repeat) polymorphisms can exclude many known adRP sites in families with five or more affected members available for testing (Sullivan et al. 2006b). In contrast, because of statistical issues, larger families are required for linkage inclusion, that is, mapping a disease gene by observing cosegregation of polymorphic markers. Since dominant retinal disease families may have many living, affected members, linkage mapping is an effective tool for localizing new adRP genes.

Contemporary marker sets for linkage mapping include hundreds of thousands of SNPs (single-nucleotide polymorphisms) such as markers in Affymetrix SNP Arrays (Friedman et al. 2009; Bowne et al. 2011a). Generally, in families with eight or more affected members available for testing, linkage mapping reduces the target region to one or a few chromosomal sites, each < 10 Mb in length. This substantially reduces the “space” to search for novel adRP

genes using NGS approaches. As an alternative to using SNP marker arrays, data from whole-exome NGS testing of multiple family members can be combined for linkage mapping in RP families based on regions identical-by-descent and shared rare variants (Koboldt et al. 2014).

Each approach is useful: Most adRP genes in Table 1 were first localized by linkage mapping; NGS methods were used to find most of the recently identified genes; and retinal capture NGS is a rapid, efficient approach to finding disease-causing mutations in known adRP genes. Taken together, advanced DNA sequencing and mapping methods have revolutionized gene discovery and mutation detection for adRP.

DETERMINING PATHOGENEITY OF adRP MUTATIONS

Determining which of the many rare variants in our genomes are pathogenic and which are benign, with all possibilities in between, is one of the fundamental problems in medical genetics (MacArthur et al. 2014). Dominant Mendelian diseases such as adRP offer the advantage of segregation testing to evaluate pathogenicity. However, this is only one of multiple steps in establishing causality. Although there is no fully accepted protocol, each of the NGS publications cited above follows similar strategies. Note that establishing pathogenicity overlaps with, but is distinct from, the “pipeline” for sequence assembly and detection of variants. Also, criteria for establishing pathogenicity of variants that may cause autosomal dominant diseases are distinct from criteria for recessive and X-linked diseases. With these caveats in mind, the following are reasonable steps for determining pathogenicity of potential adRP mutations (not necessarily in order), using retinal capture NGS as a model.

- Although the model assumes efficient retinal capture and a patient with autosomal inheritance, it is prudent to confirm coverage of the most common adRP genes, such as rhodopsin (RHO) and PRPH2, and to consider X-linked inheritance in the absence of male-to-male transmission.



- The filtering pipeline should flag all variants with an allele frequency of $<0.1\%$ in publicly available databases such as 1000 Genomes, ESP, and dbSNP (Abecasis et al. 2012; Fernandez-Suarez et al. 2014; NCBI 2014). Note that some recessive RP mutations have population frequencies $\geq 0.1\%$, whereas all reported adRP mutations are more rare.
- Determine if any flagged variants are known, published disease-causing mutations. This requires searching, for example, relevant Leiden databases (Cremers et al. 2014), the HGMD database (HGMD 2014), and ClinVar (NCBI 2014). In-house databases should be consulted too, of course. Caution: Even though a variant is listed in a disease database, it may not be pathogenic. For uncertain variants, it is essential to confirm pathogenicity based on original publications.
- If there is no unequivocally pathogenic variant in a known adRP gene, consider deletion detection for PRPF31 (Sullivan et al. 2006b) and/or nested Sanger sequencing of ORF15 of RPGR (Churchill et al. 2013).
- In the remaining cases, rank variants by pathogenicity scores using publically available services such as PolyPhen, SIFT, NNSplice, and Mutation Taster (Schwarz et al. 2010; Knecht and Krawczak 2014). Published functional data on specific genes may be useful too.
- Confirm plausible mutations by conventional sequencing and test for segregation in available family members.
- Finally, *based on the totality of information available*, including all of the above, plus clinical information, family history, and the biology and clinical phenotypes of possible disease genes, score putative mutations (one or more) for the likelihood of causing disease in the patient and family tested. Several scoring systems have been suggested, largely ranging from “recognized cause of disorder,” “expected cause of disorder,” “may or may not cause disorder” (VUS), to “probably not causative” (Richards et al. 2008).

What do these NGS strategies miss? Mutations in known retinal disease genes outside of exons, mutations in novel genes, and mutations not detectable by shotgun sequencing (e.g., variable repeats), among others.

PREVALENCE OF DISEASE-CAUSING MUTATIONS IN adRP FAMILIES

Our research has focused principally on genetic studies of adRP patients and families. For purposes of tracking progress in gene discovery and mutation detection, we have established a cohort of well-characterized adRP families (Sohocki et al. 2001; Sullivan et al. 2006a; Bowne et al. 2008, 2013). Families in the cohort have a clinical diagnosis of adRP by a knowledgeable clinician, three or more affected generations with affected females, or two or more generations with male-to-male transmission (to bias against X-linked RP). Currently, there are 270 families in the cohort (Table 2). The families are largely Americans of European origin, 75% white, 5% African American, 5% Hispanic, 3% Asian, and the remainder other or unknown.

We have applied a variety of methods to detect disease-causing mutations in these families including linkage mapping (Sullivan et al. 1999; Bowne et al. 2002, 2011a), conventional Sanger sequencing (Bowne et al. 1999, 2006, 2008, 2013; Sullivan et al. 1999; Sohocki et al. 2001; Gire et al. 2007; Friedman et al. 2009), NGS (Bowne et al. 2011b; Wang et al. 2013), deletion detection (Sullivan et al. 2006b), and subclone sequencing of RPGR ORF15 (Churchill et al. 2013). Recently, we reported a novel adRP gene, hexokinase 1 (HK1), with a missense mutation in five independently ascertained families (Sullivan et al. 2014). This gene, too, was tested in the cohort.

Table 2 summarizes our findings. To date we have identified the disease-causing mutation in 78% of the families, leaving 22% in which the known dominant RP genes have been excluded. Figure 1 shows the fraction of cases caused by mutations in each gene.

Note that Table 2 includes mutations in two X-linked genes, RPGR and RP2, found in a total of 25 families (9%). Each of these families met

Table 2. Prevalence of disease-causing mutations in adRP families (N = 270), with number of mutation types

Gene	Families	Percent	Missense	Nonsense	Other
CRX	2	0.7	1	0	1
HK1	3	1.1	1	0	0
IMPDH1	10	3.7	2	0	0
KLHL7	3	1.1	3	0	0
NR2E3	6	2.2	1	0	1
NRL	2	0.7	2	0	0
PRPF3	4	1.5	2	0	0
PRPF31	24	8.9	4	3	17
PRPF8	7	2.6	4	0	1
RDH12	1	0.4	0	0	1
PRPH2	19	7.0	10	1	2
PRPH2+ROM1	1	0.4	1	0	1
RHO	83	30.7	30	2	1
RP1	13	4.8	0	3	1
RP2	3	1.1	1	0	2
RPE65	1	0.4	1	0	0
RPGR	22	8.1	4	2	13
SNRNP200	4	1.5	4	0	0
TOPORS	4	1.5	3	0	1
None	58	21.5			
Total	270	100			

reasonable criteria for inclusion in a cohort of “autosomal dominant” families, with multiple affected females and an initial diagnosis of adRP. On further review, most, but not all, affected females are more mildly affected than age-matched affected males (Wu et al. 2010; Churchill et al. 2013). Clinical symptoms are also more variable in carrier females, consistent with Lyonization or other factors modifying expression. This is an example of the power of molecular findings to dramatically change an initial diagnosis.

Based on the significant fraction of X-linked mutations among families with a diagnosis of adRP, mutations in RPGR are probably the most common cause of RP in the world. This is reinforced by the finding that RPGR mutations account for 13% of isolated RP in males (Branham et al. 2012).

The cohort families also have one instance of digenic inheritance of a PRPH2 Leu185Pro mutation combined with a ROM1 Leu114fs*131 mutation (Kajiwara et al. 1994; Sullivan et al. 2006a). Technically, the inheritance pattern deviates from classical adRP because an affected

child must inherit both alleles from an affected parent, or one allele from an unaffected parent. This is a rare condition but other ROM1 (rod outer-membrane protein 1) mutations are known to cause digenic RP in combination with the PRPH2 Leu185Pro mutation (Dryja et al. 1997).

Table 2 also indicates the distribution of mutation types in three broad classes, missense, nonsense, and “other.” From a functional perspective, missense mutations are likely to produce an abnormal protein and the mode of action is through partial loss-of-function, gain-of-function, dominant negative, or toxic effects. “Other” mutations most likely result in functional haploinsufficiency, that is, no protein or a nonfunctional protein. Nonsense mutations may or may not produce a protein depending on whether the premature stop is in the last exon, which escapes nonsense mediated decay, or earlier exons, which do not. Based on Table 2, most adRP mutations do not result in functional haploinsufficiency, except for PRPF31.

A substantial fraction of mutations detected in the cohort are “common,” that is, they occur

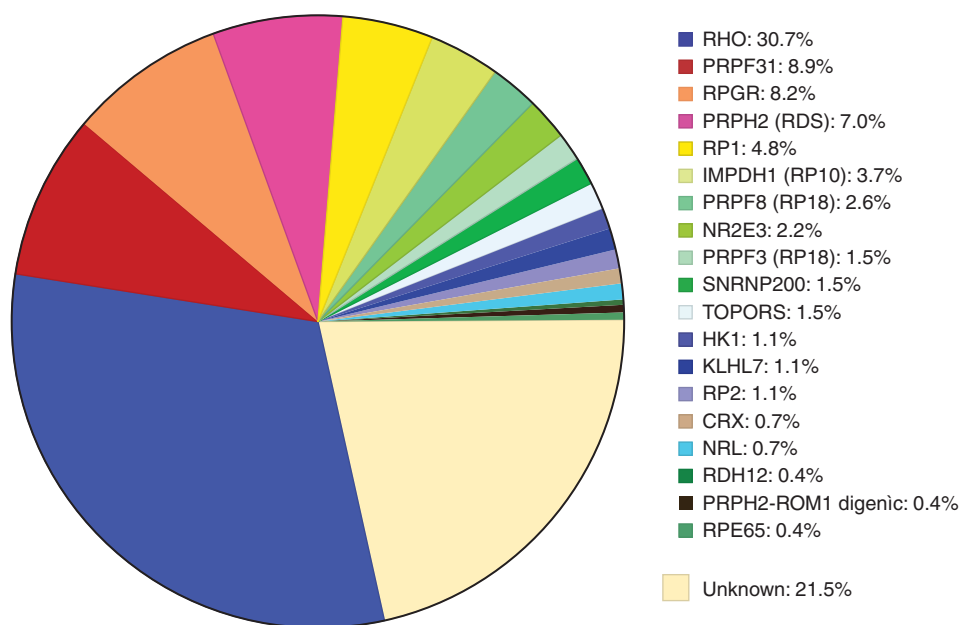


Figure 1. Fraction of mutations causing dominant RP in a cohort of 270 “adRP” families.

in three or more unrelated families. Table 3 lists the common mutations and the fraction of families with each. Twelve mutations in adRP genes account for nearly 30% of these families (i.e., excluding RPGR and RP2). Most of these mutations are ethnic-specific. Several arose by founder effect and have limited geographic distribution. That is, the mutation arose once only, increased in frequency by drift and population dynamics, and shares a distinct haplotype in *cis* to the mutation. For example, the rhodopsin Pro23His mutation (13%) and the peripherin 828+3A>T mutation (2%) arose by founder effect, are almost exclusive to the United States, and are found only in Americans of European origin (Dryja et al. 1990, 1991; Shankar et al. 2004). The hexokinase Glu847Lys mutation also arose from a common ancestor, but the mutation is found in North America and Europe (Sullivan et al. 2014). In contrast, the Asp226Asn mutation in the inosine monophosphate dehydrogenase 1 gene (IMPDH1) arose independently on multiple occasions (Sullivan et al. 2006a).

This is a general phenomenon for RP mutations: the prevalence of mutations in a given

gene is often dominated by one or a few mutations that arose by founder effect. Thus, populations will have different prevalences as a result of founder mutations, even though the RP genes are universal and the fraction of new mutations is roughly the same worldwide. For example, rhodopsin mutations account for 30% of adRP cases among Americans of European origin but

Table 3. Common mutations in adRP genes and RPGR ($N = 270$)

Gene	Families	Mutation	Percent
HK1	3	Glu847Lys	1.1
IMPDH1	6	Asp226Asn	2.2
	4	Asp311Asn	1.5
NR2E3	5	Gly56Arg	1.9
PRPF3	3	Thr494Met	1.1
PRPH2	5	828+3A>T	1.9
	4	Pro216Ser	1.5
RHO	5	Arg135Leu	1.9
	5	Arg135Trp	1.9
	36	Pro23His	13.2
RP1	6	Arg677X	2.2
	4	Leu762Tyrfs*17	1.5
RPGR	3	Glu802Glyfs*32	1.1
Total			33.0

<10% in China, largely because the Pro23His mutation is absent from China (Li et al. 2010). In contrast, the prevalence of RPGR mutations, which are predominantly new mutations, is roughly the same worldwide (Bocquet et al. 2013; Xu et al. 2014).

DOMINANT-RECESSIVE ACTING adRP MUTATIONS

In most cases in which a gene in Table 1 has more than one disease association, this is the result of different mutations in the same gene causing different diseases. However, there are two instances in which the same mutation has different consequences depending on whether one or two copies are present, that is, whether the patient is heterozygous or homozygous. Technically, these mutations are dominant *and* recessive acting. In one large adRP family with the RP1 Arg677X mutation, two homozygous individuals are severely affected whereas heterozygous individuals are more mildly affected (Sullivan et al. 1999). In contrast, the consequences of this mutation are distinct from clinical expression of the several RP1 mutations, which are truly recessive, with unaffected carriers (Khaliq et al. 2005; Riazuddin et al. 2005). Similarly, in a large adRP family with the HK1 Glu847Lys mutation, a single homozygous individual is significantly more severely affected than heterozygotes (Sullivan et al. 2014). These cases may be rare, but because members of large, multigenerational adRP families occasionally live in the same community, this is more likely with adRP than with other dominant diseases.

NORMAL FUNCTION OF adRP GENES

Table 1 provides a brief phrase describing the functional class of each gene. Excellent, extensive reviews are also available (Berger et al. 2010; Wright et al. 2010). Even limiting discussion to genes that account for 1% or more of cases, genes causing adRP have diverse functional roles.

It is not surprising that mutations in genes coding for proteins that are abundant in rods or play fundamental roles in photoreceptor function may cause dominant RP. This includes

rhodopsin, the most abundant rod protein; peripherin (PRPH2) and ROM1, which are essential structural components of rod outer membranes; and rod/cone expression factors such as CRX, NRL, and NR2E3. Mutations in these genes are frequent causes of adRP. On the other hand, the relationship between function and disease of other adRP genes is less clear.

For example, the protein products of four adRP genes, PRPF3, PRPF8, PRPF31, and SNRNP200, are essential components of the U4/U6-U5 tri-snRNP complex of the spliceosome involved in mRNA splicing (Liu and Zack 2013). The products of two less frequent causes of adRP, PRPF4 and PRPF6, are also components of this complex. These genes are expressed in all tissues and are highly conserved in all eukaryotes. Why mutations in these genes cause dominant RP, and only RP, is not known. However, genes coding for other proteins in this complex are attractive candidates for novel adRP genes.

The protein products of the remaining common adRP genes, HK1, IMPDH1, KLHL7, RP1, and TOPORS, are enzymes found in all cells (HK1 and IMPDH1), have a universal role in protein degradation (KLHL7), or are components of sensory cilia (RP1). That is, their roles are diverse and not obviously predictive of dominant, degenerative disease limited to the retina.

RECONCILING CLINICAL DIAGNOSIS, FAMILY HISTORY AND MOLECULAR FINDINGS

An emerging realization in inherited retinopathies is apparent discrepancies between clinical findings, inheritance pattern, and results of genetic testing. Clinical findings of retinitis pigmentosa and evidence from family history of dominant inheritance are consistent with a diagnosis of adRP. Fortunately, in most cases, a diagnosis of adRP is supported by the results of genetic testing. However, given the complex relationship between genes, mutations, and inherited retinopathies, there are opportunities for conflicts, for instance, when an apparent disease-causing mutation is in a gene not known to cause adRP, or the clinical phenotype in the family is more variable than just RP, or the ap-



parent mode of inheritance is misleading or not determined. For these reasons, clinicians, counselors, and geneticists must work closely with each other to resolve these conflicts. In some cases, a reconsideration of the clinical, family, and molecular findings, taken together, may substantially alter the predicted mode of inheritance and prognosis. Thus, in addition to all the other benefits of genetic testing of patients with RP, molecular findings may substantially alter diagnosis, prognosis, counseling, and treatment.

CONCLUDING REMARKS

The long-term objective of research on genes and mutations causing inherited retinopathies is to enable effective genetic testing of patients and families, to incorporate this information into clinical care and counseling, and to develop treatments and cures based on a fundamental understanding of disease pathology. Currently, the success rate for finding the causative mutation in adRP patients is 50%–75%, but this fraction will increase rapidly with widespread adaptation of NGS testing and development of “third-generation” sequencing (Laszlo et al. 2014). Gene-specific and mutation-specific treatment trials have begun already. In time the limitation will not be genetic testing per se, but interpretation of variants, reconciling diagnosis and molecular findings, and providing meaningful information to clinicians and useful counseling to patients. The realization of these goals requires close integration of retinal specialists, genetic counselors, molecular geneticists, and bioinformaticists.

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