A Review of Secondary Photoreceptor Degenerations in Systemic Disease

Naveen Mysore^{1,2}, Jamie Koenekoop², Shen Li², Huanan Ren², Vafa Keser², Irma Lopez-Solache², and Robert K. Koenekoop^{1,2,3,4}

¹Department of Paediatric Surgery, Human Genetics and Ophthalmology, McGill University, Montreal, Quebec H3A 1A1, Canada

²McGill Ocular Genetics Laboratory, Montreal, Quebec H3H 1P3, Canada

³Faculty of Medicine, Human Genetics, McGill University, Montreal, Quebec H3A 1B1, Canada

⁴Montreal Children's Hospital Research Institute, Montreal, Quebec H3H 1P3, Canada

Correspondence: robert.koenekoop@mcgill.ca

Photoreceptor neuronal degenerations are common and incurable causes of human blindness with one in 2000 affected. Approximately, half of all patients are associated with known mutations in more than 200 disease genes. Most retinal degenerations are restricted to the retina (primary retinal degeneration) but photoreceptor degeneration can also be found in a wide variety of systemic and syndromic diseases. These are called secondary retinal degenerations. We review several well-known systemic diseases with retinal degenerations (RD). We discuss RD with hearing loss, RD with brain disease, and RD with musculoskeletal disease. We then postulate which retinal degenerations may also have previously undetected systemic features. Emerging new and exciting evidence is showing that ubiquitously expressed genes associated with multitissue syndromic disorders may also harbor mutations that cause isolated primary retinal degeneration. Examples are *RPGR*, *CEP290*, *CLN3*, *MFSD5*, and *HK1* mutations that cause a wide variety of primary retinal degenerations with intact systems.

RETINAL DEGENERATION AND SYSTEMIC DISEASE

Photoreceptor degeneration leads to blindness in millions of people and is thought to have a worldwide prevalence of one in 2000. Photoreceptor death and pigmentary retinal degeneration is the final common outcome in many retinal disorders (such as retinitis pigmentosa, RP) and many choroidal disorders

(such as choroideremia), but it is also a common and serious manifestation of numerous metabolic, neuro-degenerative and other systemic diseases.

The evaluation of patients with pigmentary retinal degeneration is especially challenging for various reasons. First, the retinal degenerations can be found in babies and infants, and dominate the phenotype early in the disease process, whereas life threatening systemic disease follows

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later. Second, the retinal appearance, although highly variable even within families, does not predict the genetic lesion, nor the systemic disease as the fundus picture may represent a primary eye disease, a harbinger of impending neurological disease, a remote effect of cancer, or the beginning of a full blown systemic disease. Third, the genetic heterogeneity underlying primary and secondary photoreceptor degenerations is astounding and unexpected. There are currently 260 gene or loci associated with retinal degenerations. Fourth, as a result of intense genetic, genomic, proteomic, and therapeutic research, this exciting field is rapidly changing and new concepts about the relationship between genotype and phenotype are emerging. Examples of these new concepts will be discussed in this article and include retinal diseases that were thought to be confined to the retina, but after careful phenotyping, turned out to be systemic diseases. That is, *RPGR* mutations cause X-linked RP, but were later found to associate with and cause hearing loss and sinus disease. A second new concept is the emergence of the new knowledge that ubiquitously expressed genes, associated with multisystem systemic disease, can be mutated and associated with primary retinal degeneration without the systemic features. *CEP290* mutations are an important cause of Joubert syndrome, a systemic neurological disorder. Hypomorphic alleles in *CEP290* have been identified as the most common cause of Leber congenital amaurosis (LCA), a primary photoreceptor degeneration (den Hollander et al. 2006).

The retinal dystrophies with a systemic component (sometimes called secondary retinal dystrophies or secondary pigmentary retinopathies) are extensive. We will review three categories of retinal degenerations (RD) with systemic diseases: (1) hearing loss with RD; (2) musculoskeletal disease with RD; and (3) central nervous system (CNS) disease with RD. We will then discuss several eye diseases that turn out to be systemic diseases, followed by a discussion of four ubiquitously expressed genes associated with multisystem disease that were recently found to harbor hypomorphic alleles

that cause primary photoreceptor degeneration without the systemic disease.

SYSTEMIC DISEASE WITH SECONDARY RETINAL DEGENERATION

Hearing loss with pigmentary retinopathy are seen with the systemic diseases Usher syndrome (USH), Alström disease, and Refsum disease. Hearing loss is caused by loss or dysfunction of auditory hair cells, whereas vision impairment is caused by death and dysfunction of photoreceptor cells. Both cells are related, are modified ciliated cells from ciliated progenitor cells and their shared vulnerability in many important diseases is not a surprise or coincidence.

USH is the most common form of inherited deaf (hearing loss)-blindness with a worldwide prevalence of nearly one in 6000. Three clinical subtypes (USH1, USH2, and USH3) are defined according to the severity of the hearing impairment, the presence of vestibular dysfunction (ataxia), and the age of onset of the RD, in which type I is profound, type II is partial, and type III is acquired and progressive. All are inherited in an autosomal recessive manner. All three types are genetically heterogeneous conditions and currently 12 USH genes and three loci have been described (see <https://sph.uth.edu/retnet/>). Genetic complexity is also exhibited in the fact that USH mutations can cause diverse diseases, and genotype–phenotype correlations are not straightforward. For example, USH2A mutations can cause Usher syndrome type 2 (USH2), nonsyndromic RP without hearing loss, and nonsyndromic deafness without blindness, sometimes in the same family (Chen et al. 2014).

The Usher gene products localize to the connecting cilium and periciliary regions of photoreceptors and hair cells, and the Usher proteins form a proteomic network. Photoreceptors, auditory hair cells, and vestibular hair cells develop from ciliated progenitors and are therefore all affected by mutations in Usher proteins. Sperm motility may also be affected, leading to infertility. A generalized abnormality of all Usher disease patients is a ciliary abnormality specifically caused by the cytoskeletal structures

of cilia. In mature hair cells of the ear, the disease is likely caused by defects in the Usher proteins that anchor the taller stereocilia's actin cytoskeleton core to the shorter adjacent stereocilia and to the mechanotransduction channels. All the USH1 and USH2 proteins are organized into a protein network by harmonin, whirlin, and SANS (Sorusch et al. 2014). This new proteomic information has contributed greatly to our currently improved understanding of USH protein function in the eye and the ear, and partly explains why defects in proteins of different families cause very similar phenotypes, unlike RP in which the causal genes have a wide variety of different functions (Sorusch et al. 2014). The Usher protein interactome at the periciliary region of the photoreceptor outer segment suggests that Usher proteins regulate protein trafficking between the inner and outer segments of photoreceptors as well as cytoskeletal functions and roles in molecular transport processes and ciliary cargo delivery in photoreceptor cells. USH is thus related to other ciliopathies, including nonsyndromic inner ear defects and isolated retinal dystrophies but also to kidney diseases and syndromes like the Bardet-Biedl syndrome. USH is therefore a "ciliopathy," molecularly related to other ciliopathies, which may open an avenue for common therapy strategies for all ciliopathies.

Currently, there is no treatment for Usher patients, other than augmentation of hearing with hearing aids. Oral antioxidants may slow down retinal disease progression. There is no definitive treatment for the sensory-neuronal degeneration of the eye. In very exciting new developments, gene-based therapies to halt, slow down, or cure the retinal degeneration of USH1 patients are being studied (Nagel-Wolfrum et al. 2014). Three different avenues are currently being tested: (1) USH retinal gene augmentation using recombinant adeno-associated virus; (2) genome editing by homologous recombination mediated by zinc-finger nucleases (ZFN) (Overlack et al. 2012); and (3) read-through therapy using novel designer amino glycosides (Nagel-Wolfrum et al. 2014), as in-frame nonsense mutations account for ~20% of all USH cases. These exciting therapies are slowly entering hu-

man clinical trials, and may be applicable to a wide range of ciliopathies, beyond USH. These developments can be followed on the clinical trials web site (see <https://clinicaltrials.gov/ct2/search>).

Alström disease is an autosomal recessive systemic single gene disorder, caused by mutations in *ALMS1* (2p13). Alström syndrome is a severe, early onset, progressive but variable multisystemic disease, with cone-rod retinal degeneration leading to juvenile blindness, sensorineural hearing loss, obesity, insulin resistance with hyperinsulinemia, and type 2 diabetes mellitus. Very high incidences of additional disease phenotypes that may severely affect prognosis and survival include endocrine abnormalities, dilated cardiomyopathy, pulmonary fibrosis and restrictive lung disease, and progressive hepatic and renal failure. Other clinical features in some patients are hypertension, hypothyroidism, hyperlipidemia, hypogonadism, urological abnormalities, adult short stature, and bone-skeletal disturbances. Most patients show normal intelligence, although some reports indicate delayed psychomotor and intellectual development (Marshall et al. 2007). The visual loss can be so severe and congenital, that it is possible to diagnose a child with severe visual loss at birth, nystagmus and normal systemic features as LCA, and subsequently see the later development of the multisystem disorder and thus Alström syndrome.

The clinical diagnosis of Alström syndrome in an infant or very young child requires the presence of a characteristic infancy onset retinal dystrophy with photodysphoria and either obesity or cardiomyopathy. In childhood, early adolescence, and adulthood, additional phenotypes evolve. Insulin resistant diabetes can occur from puberty and may be preceded by acanthosis nigricans. Triglycerides are often elevated. Many patients develop cardiomyopathy in infancy or adolescence. Recurrent lower respiratory tract infections are common in early childhood and nonalcoholic fatty liver disease develops during puberty. Chronic renal failure is seen in up to 25% of patients during the second decade. Multiple organ fibrosis is found at postmortem (Marshall et al. 2011). Recent-

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ly, the protein product of the Alström gene, *ALMS1*, has also been localized to cilia and been implicated in endosome trafficking and recycling. Impaired endosome recycling has an impact on cell division, and internalization of protein and lipid products based on external cues (Collin et al. 2012). There have been 98 different disease-causing mutations described thus far including nonsense (49%), indels (43%), frameshifts, and splice site alterations (3%). Both mutations are found in 63% of patients; in 33% only one mutation is found, and in 4% no mutations are found (Marshall et al. 2011).

Finally, classic or adult onset Refsum disease (OMIM 266500) was first described by Norwegian neurologist Sigvald Refsum. It represents an autosomal recessive inborn error of lipid metabolism, classically characterized by a pentad of clinical abnormalities: pigmentary retinal degeneration; hearing loss; peripheral neuropathy; cerebellar ataxia; and elevated protein levels in the cerebrospinal fluid (CSF) without an increase in the number of cells. However, not all patients show all these features. All patients have accumulation of an unusual branched-chain fatty acid and phytanic acid in blood and tissues due a deficiency in phytanoyl-CoA hydroxylase, which is caused by mutations in *PHYH*. Other variable features include cardiac dysfunction, ichthyosis, and multiple epiphyseal dysplasia. Hence, the above clinical features are the result of a buildup of phytanic acid in neurons. As cilia (Usher and Alström) and phytanoyl-CoA hydroxylase (Refsum) are ubiquitous structures and enzymes respectively, it makes sense that these entities are systemic diseases with secondary photoreceptor degenerations. Increased levels of phytanic acid can also be found in the blood and tissues of peroxisomal biogenesis disorders, among which is the infantile Refsum disease (OMIM 601539), a distinct disorder with a different phenotype and a different genotype. However, a phenotype clinically indistinguishable from that of classic Refsum disease (OMIM 614879) but with a different biochemical profile, can be caused by mutation in the gene encoding peroxin-7 (*PEX7*) on chromosome 6q.

Eldjarn and colleagues showed that with a diet free of chlorophyll and other foods, which might contain phytol or phytanic acid, the levels of phytanic acid could be reduced in the blood and the clinical improvements can be documented (Eldjarn et al. 1966). Also, plasmapheresis performed once or twice a month can effectively remove phytanic acid from the body and prevents progression of the clinical features (Gibberd et al. 1979).

The musculoskeletal diseases with pigmentary retinopathy are usually associated with mitochondrial defects and therefore exhibit mitochondrial inheritance (maternal). The disease entities include Kearns–Sayre syndrome and mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS). Kearns–Sayre syndrome includes chronic progressive external ophthalmoplegia, pigmentary retinopathy, cardiac arrhythmia, cerebellar ataxia, and dementia. MELAS is associated with elevated lactic acid, sensorineural hearing loss, Wernicke’s aphasia, encephalopathy, and seizures. The mtDNA deletions that cause Kearns–Sayre syndrome result in the loss of genes important for mitochondrial protein formation and oxidative phosphorylation. The most common deletion removes 4997 nucleotides, which includes 12 mitochondrial genes. Deletions of mtDNA result in impairment of oxidative phosphorylation and a decrease in cellular energy production.

While Kearns–Sayre has typical tapetoretinal degeneration, MELAS shows a diffuse granular and choriocapillaris loss. There is significant outer retinal thinning (de Laat et al. 2013) and in vivo retinal imaging by optical coherence tomography (OCT) show occasional ovoid retinal structures with hyperreflective borders. Mutations in a particular transfer RNA gene, *MT-TL1*, cause >80% of all cases of MELAS. These mutations impair the ability of mitochondria to make proteins, use oxygen, and produce energy. Because mitochondria are found in all the cells of the human body, these defects are expected to cause multisystem disease including the photoreceptors.

The CNS conditions associated with pigmentary retinopathies are Abetalipoproteinemia

mia, Bardet–Biedle syndrome (BBS), Joubert syndrome, Laurence–Moon syndrome (LMS) and neuronal ceroid lipofuscinosis (NCL).

Abetalipoproteinemia (or Bassen–Kornzweig syndrome, BKS) is a monogenic, rare disease with a prevalence of one in a million caused by malabsorption of vitamins A and E in the small intestines. BKS is characterized by fat malabsorption, acanthocytosis, and hypcholesterolemia in infancy, with later development of a severe deficiency of fat soluble vitamins and subsequent development of atypical retinal degeneration, coagulopathy, posterior column neuropathy, and myopathy. BKS is an autosomal recessive systemic condition owing to homozygous or compound heterozygous mutations in *MTTP* gene, which encodes the microsomal triglyceride transfer protein, essential for creating beta-lipoproteins. MTTP plays a critical role in the liver and the formation of hepatic very low-density lipoproteins. Lipoproteins are essential for absorption of fats, cholesterol, and fat-soluble vitamins (A and E) from the diet. In BKS, the *MTTP* mutations result in decreased production of beta-lipoproteins in the body, and therefore poor uptake of essential vitamins A and E. Ultra-long-term intake of high dose oral vitamins, including A, E, and K has been documented to slow the progression of the neurological and the retinal degenerative diseases.

Bardet–Biedle syndrome (BBS) is an autosomal recessive and genetically heterogeneous systemic syndrome associated with mental or behavioral abnormalities, truncal obesity, polydactyly, hypogonadism, severe renal dysfunction (nephrogenic diabetes insipidus), and retinal degeneration. Although there are multiple genes (currently 18 genes have been described that settle ~70%–75% of the BBS patients) associated with BBS, fundamentally the phenotype is a result of ciliary dysfunction. There are currently two known BBS protein complexes, the BBSome consisting of seven known BBS proteins, and the BBS chaperone complex consisting of three known BBS proteins. The formation of the BBSome requires the function of the BBS chaperone complex. BBS genes exhibit ciliary function, in intracellular and intraflagel-

lar trafficking (IFT). The common primary function of BBS proteins is likely the mediation and regulation of microtubule-based intracellular and ciliary protein transport. Currently, in BBS patients, the cell types known to be impacted by the global ciliary dysfunction include renal and retinal tissues as well as the neural tube, developing limbs, pancreas, liver, spleen, bone, and several parts of the CNS (Zaghoul and Katsanis 2009). Obesity may be related to dysregulated hormonal cues for feeding (ciliary dysfunction in the hypothalamus) as well as increased adipogenesis. Cilia are required in the downstream signaling pathway for Sonic Hedgehog in limb development. In renal development, cilia are required for the cell polarity and orientation of the nephron. Ciliopathies may lead to dysfunctional neuronal migration resulting in mental retardation, however this is not very well understood. The associated retinopathy is caused by photoreceptor death secondary to connecting cilium between the inner segments of the photoreceptors, or a possible defect in vesicular transport. The Laurence–Moon syndrome is similar phenotypically to Bardet–Biedle syndrome but individuals do not have obesity and polydactyly.

Neuronal ceroid lipofuscinosis (NCL) is a group of conditions that result in accumulation of toxic lipofuscin in neuronal tissues (including the brain, retina, and peripheral nerves). NCL is inherited in an autosomal recessive manner. Infantile NCL or Santavuori disease, caused by mutations in *CLN1* begins between 6 mo and 2 yr, and is associated with muscular hypotonia, ataxia, retinal degeneration, and progressive and rapid mental deterioration. *CLN1* encodes palmitoyl protein thioesterase 1, which participates in various cellular processes, including apoptosis, endocytosis, vesicular trafficking, synaptic function, and lipid metabolism. Palmitoyl protein thioesterase 1 (PPT1) may also be involved in cell death signaling as reduced expression of PPT1 increases the susceptibility to induced apoptosis (Jalanko and Braulke 2009). Late infantile NCL or Jansky–Bielchowsky disease, caused by mutations in *CLN2* presents between the ages 2–4 yr, and has similar findings as the infantile form. *CLN2* encodes tripeptidyl peptidase 1

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(TPP1), a lysosomal hydrolase that removes tripeptides from the amino terminus of small polypeptides. The deficiency in TPP1 leads to buildup of lysosomal storage products. Juvenile NCL, caused by mutations in *CLN3* is slowly progressive, and is associated with seizures, but children have normal development. *CLN3* encodes a hydrophobic integral membrane protein. The proposed functions of *CLN3* include lysosomal acidification, lysosomal arginine import, membrane fusion, vesicular transport, cytoskeletal linked function, autophagy, apoptosis, and proteolipid modification (Jalanko and Brulke 2009). A deficiency of *CLN3* can thus lead to a buildup of lysosomal storage products. In all three conditions of NCL, optic atrophy and pigmentary retinopathy is seen. Interestingly, electron microscopy of skin cells reveals curvilinear bodies in the cytoplasm. In vivo retinal imaging by OCT of the retina shows small hyperreflective bodies at the level of the RPE.

Primary Retinal Degenerations That Are Actually Secondary Retinal Degenerations with Systemic Disease

Bietti's crystalline retinal dystrophy (BCD) is an autosomal recessive retinal degeneration having clinical overlap with choroideremia CHM. BCD represents a severe progressive retinal degeneration with retinal crystals caused by mutations in *CYP4V2*. BCD is a rare disease described by Bietti in 1937, characterized by multiple small crystalline intraretinal deposits (crystals), with retinal pigment epithelium (RPE) atrophy, pigment clumping, and choroidal sclerosis. The crystals are visible on clinical funduscopy, but eventually, as the disease worsens and progresses, the crystals become impossible to see and disappear. Initially thought to be restricted to the retina, BCD crystalline inclusions were surprisingly also found throughout the body, including in the cornea, peripheral blood lymphocytes, and skin fibroblasts, with elevations of fatty acid levels in the serum (Lee et al. 2001). With increased risk factors for cardiovascular disease, BCD has recently been redesignated as a systemic lipid metabolic disease with photoreceptor degeneration. Patients with BCD were

found to have a significantly higher concentrations of octadecanoic acid (18:0) but lower concentration of octadecadienoic acid (18:1n-9), while the total monounsaturated fatty acid concentration was significantly lower in BCD as well as lower activity of the Δ -9-desaturase enzyme (Lai et al. 2010). Similar to CHM, BCD patients exhibit severe progressive chorio-retinal atrophy and degeneration. However, unlike CHM patients, BCD patients exhibit retinal crystals on fundus exam, systemic crystals, and elevated fatty acid levels.

Having reviewed secondary retinopathies and recently added BCD to the list of secondary pigment degenerations with systemic disease, we can consider the following important question. Are there other primary retinopathies that have a systemic component? In particular, we can consider gyrate atrophy and central areolar choroidal dystrophy. Gyrate atrophy is an autosomal recessive condition, caused by mutations in *OAT*, which encodes ornithine aminotransferase, a ubiquitously expressed gene. Patients with gyrate atrophy have abnormal *OAT* activity, resulting in elevated levels of ornithine. The retinal findings include punched out round peripheral lesions, forming a scalloped border between normal and abnormal retina. Interestingly, OCT findings reveal possible subretinal crystals (ovoid bodies with hyperreflective borders) (Sergouniotis et al. 2012). Thus, there may be systemic features in gyrate atrophy as *OAT* is expressed in many tissues. Central areolar choroidal dystrophy (CACD) has an autosomal dominant inheritance pattern with mutations in the peripherin-2 (*PRPH2*) gene. Peripherin-2 is thought to play a structural role, stabilizing photoreceptor discs (Smailhodzic et al. 2011). In the early stages of the condition, spectral domain OCT shows disorganization of the photoreceptor layer with thinning of the outer retinal layers. In advanced cases, ovoid structures with similar hyperreflective borders have also been seen (Smailhodzic et al. 2011). Currently there are no observed systemic features in CACD, but the presence of these ovoid bodies, similar to those seen in BCD, may suggest the possibility of finding systemic abnormalities.

Ubiquitously Expressed Genes Associated with Complex Multitissue Systemic Disease Can Be Mutated in Primary Retinal Degeneration

RPGR Mutations Cause X-linked RP, but Can Also Cause Hearing Loss and Sinus Disease

The first and most commonly mutated gene in X-linked retinitis pigmentosa is *RPGR*, retinitis pigmentosa GTPase regulator protein gene. *RPGR* predominantly localizes to the transition zone of primary cilia and associates with selected ciliary and microtubule associated protein assemblies. The *RPGR* interactome facilitates a growing and increasing number of multiple ciliary protein complexes. *RPGR* is mutated in ~70% of X-linked RP patients and in 10%–20% of simplex RP males, two severe eye diseases confined to the retina. Recently Zito et al., Iannaccone et al. and Koenekoop have documented retinal degeneration patients and families, with significant hearing loss, and pseudo Usher disease, who also developed recurrent sinus disease (Iannaccone et al. 2003; Zito et al. 2003; Koenekoop 2004). In addition, Iannaccone et al. detected *RPGR* expression in bronchial and sinus epithelial cells. A new concept emerged that some ubiquitously expressed genes can cause isolated retinal degeneration or secondary retinal degeneration plus systemic disease. Severity, location of the mutations, the different isoforms and modifying environment, and background genetic factors may all play a role in this process.

CEP290 Mutations May Be Hypomorphic and Cause Isolated Primary Retinal Degeneration

Mutations in the gene encoding the 290 kDa centrosomal protein (CEP290) cause a surprising, wide ranging, and expanding array of debilitating human and animal diseases ranging from lethal Meckel Gruber disease (meningo-occipital encephalocele, cystic kidney dysplasia, hepatobiliary ductal plate malformation, and postaxial polydactyly), Joubert syndrome (psychomotor delay, hypotonia, ataxia, and “molar tooth sign”, indicating hypoplasia of the cerebellar vermis, nephronophthisis and retinal dys-

trophy), Senior–Loken syndrome (nephronophthisis and retinal degeneration), and Bardet–Biedle syndrome (obesity, psychomotor delay, retinal degeneration, polydactyly, hypogonadism, and renal abnormalities). *CEP290* mutations were also discovered to be the most important and frequent cause of isolated blindness in Leber congenital amaurosis (den Hollander et al. 2006). *CEP290* positive LCA patients have no systemic disease. The type, severity, and location of the mutations in *CEP290* do not explain the diversity of associated phenotypes (den Hollander et al. 2006).

How can mutations in a gene be associated with severe multisystem disease, whereas other mutations in the same gene cause isolated retinal degeneration? How the many identified mutations in *CEP290* contribute to these diverse pathologies ranging from lethal multitissue disease to isolated retinal blindness remains unknown, and the protein’s normal biological role has not been well characterized. One possibility is the existence of hypomorphic alleles. In the original LCA family with the first *CEP290* mutations, it was found that notably in affected patients’ lymphoblastoid cell lines harboring the common c.2991 + 1655A → G mutation, a small amount of wild-type *CEP290* protein product was found. This suggests that this is a hypomorphic allele, harming the retina but not the other tissues in which *CEP290* is expressed (den Hollander et al. 2006).

Another explanation may be that different domains and their inactivation by mutations cause different disease entities. Drivas et al. (2013) discovered four new functional domains of the *CEP290* protein. They found that *CEP290* directly binds to the cell membranes, through an amino-terminal domain that includes a highly conserved motif, and to microtubules, through a domain located within its myosin-tail homology domain. They also identified that *CEP290* activity was regulated by two novel auto inhibitory domains within both the amino and carboxyl termini, both of which were found to play critical roles in regulating ciliogenesis (Drivas et al. 2013). Disruption of the microtubule-binding domain in a mouse model (rd16) of LCA was sufficient to induce significant

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deficits in cilium formation, which led to isolated retinal degeneration. Drivas et al. (2013) showed that CEP290 is a crucial integral structural and regulatory component of the cilium. Further, their data illustrate, for the first time, that disruption of particular CEP290 functional domains lead to particular disease phenotypes. Also, truncation mutants of CEP290 lacking the inhibitory domains but maintaining the other functional regions of the protein may exhibit normal, or even enhanced, CEP290 function allowing for truncated therapeutic packages delivered by viral vectors such as AAV (Drivas et al. 2013).

In another development, Burnight et al. (2014) report the development of lentiviral vectors carrying full-length *CEP290* for the purpose of correcting the CEP290 disease-specific phenotype in human cells. A lentiviral vector containing CMV-driven human full-length *CEP290* and transduced in iPSC-derived, photoreceptor precursor cells. As CEP290 is important in ciliogenesis, the ability of fibroblast cultures from CEP290-associated LCA patients was tested. They show, for the first time, that lentiviral delivery of CEP290 rescued the ciliogenesis defect.

CLN3 Mutations Can Cause Isolated Primary Retinal Degenerations

CLN3 mutations are known to cause Batten disease, a devastating multitissue disease with neurodegeneration and intracellular accumulation of autofluorescent lipopigment storage material causing progressive dementia, seizures, and progressive visual failure. The *CLN3* gene product may function as a chaperone involved in the folding/unfolding or assembly/disassembly of other proteins, specifically subunit c of the ATP synthase complex. It is expressed ubiquitously, especially strong in the brain and neurons. Wang et al. (2014) found *CLN3* mutations in five isolated retinal degeneration patients, with normal brain and neurological systems. The patients were followed until late adulthood. Wang et al. (2014) suggest that these alleles are hypomorphic, causing retinal disease without affecting the other tissues.

MFSD8 Mutations Can Cause Primary Macular Dystrophy

MFSD8 mutations are well known causes of late infantile neuronal lipid fuscinos (NCL). Roosing et al. (2014) found *MFSD8* mutations in isolated retinal degeneration patient without systemic disease. They identified variants in *MFSD8* as a novel cause of nonsyndromic autosomal recessive macular disease. Affected individuals showed no neurological features typical for the very late-infantile form of NCL. They propose a (“gene dosage”) genotype–phenotype model in which a combination of a severe and a mild variant cause nonsyndromic macular disease, while two severe mutations cause very late infantile neuronal ceroid lipofuscinosis (Roosing et al. 2014).

HK1 Mutations Cause Dominant Retinitis Pigmentosa

HK1 encodes hexokinase 1, a well-known ubiquitous enzyme in the glycolytic pathway of all cells, which catalyzes phosphorylation of glucose to glucose-6-phosphate. *HK1* mutations have been found in nonspherocytic hemolytic anemia. Sullivan et al. (2014) recently found dominant *HK1* mutations in autosomal dominant retinitis pigmentosa in five families. They hypothesize that the effect of this mutation is limited to the retina, as no systemic abnormalities in glycolysis were detected and that *HK1* has a novel function in retina (Sullivan et al. 2014).

In summary, in the study of primary and secondary retinal degenerations and their relationship, several new trends are emerging. Primary photoreceptor degenerations without systemic features are caused by a large number of genes that are crucial to retinal development, functioning, or maintenance. Many genes solely expressed in the eye or retina will not have systemic features, but genes that are expressed elsewhere may in fact cause systemic disease in previously thought to be isolated retinal disease. Bietti crystalline dystrophy represents an example of a primary retinal degeneration that is now known to be a systemic disease with secondary

retinal degeneration. Other primary retinal degenerations may follow suit, as choroideremia and gyrate atrophy may also be secondary retinal degenerations. In a second new emerging theme, the opposite may also be true. Ubiquitously expressed genes associated with well-known multitissue syndromic disorders (NCL, BBS, JBT, SL, and others) may harbor mutations that cause isolated primary retinal degeneration. *RPGR*, *CEP290*, *CLN3*, *MFSD8*, and *HK1* are examples of recently identified ubiquitous genes that can cause primary isolated X-linked RP, LCA, arRP, arCRD, or adRP, respectively.

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