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Animals Models of Inherited Retinal Disease

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Abstract

Inherited retinal diseases (IRDs) are an important cause of blindness worldwide. Over 270 genes have been associated with IRD. Genetic testing can determine the cause of the clinical disease in the majority of patients. However, at least 25-50% of patients with clinical diagnosis of IRD remain unsolved even after whole genome sequencing. Animal models of IRD can be useful for expanding the set of established IRD genes, to gain biological understanding of the function of these genes in the retina, and to test advanced therapeutics prior to human clinical trials. In this chapter some small and large animal models of IRD are discussed including some of the advantages and limitations of each for various forms of retinopathy.

Introduction

Spontaneously occurring animal models of retinal disease and genetically manipulated mice have been an important resource not only to test gene therapies, but also to discover novel inherited retinal disease (IRD) genes in the mammalian retina. Spontaneous mutations affecting the retina have been described in many species, though single gene knockout (KO) technology has been chiefly applied to mice. Many of the ~24,380 protein-coding genes in the mouse genome have been deleted and the knockout mice phenotyped. Identification of retinal disease genes in animals provides candidate human retinal disease genes potentially relevant to patients. The candidates revealed in knockout mice can then be evaluated for human relevance by human IRD clinicians in their “unsolved” patient populations with presumed IRD for whom genetic sequencing has failed to provide a molecular diagnosis. It should be noted that in the past three decades the genetic basis of many forms of inherited retinal diseases have been discovered leading to the identification of over 270 retinal disease genes. However, in spite of the tremendous progress that has been made, the identification of the causative genetic alteration can be identified in only 50-75% of patients with presumed inherited retinal disease, even after whole genome sequencing.[1] Some of these 25-50% of IRD patients who remain “unsolved” have mutations in unknown retinal disease genes which remain to be discovered. With the advent of gene therapy and the potential for therapeutic gene editing, exciting new treatment options may be available in our lifetime. However, “unsolved” patients will necessarily be excluded from the gene therapy/editing revolution that promises to provide hope of vision saving treatments for patients afflicted with these conditions. The large fraction of unsolved cases implies there are significant

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numbers of unknown retinal diseases genes. One method of identifying the remaining retinal diseases genes is to perform whole genome sequencing (WGS) on as many human IRD patients as possible and to delve deeply into their genomes in an unbiased fashion to identify novel retinal diseases genes. However, this method depends on unbiased examination of the entire human genome, some 19,000-25,000 protein coding sequences.[2] Even if all IRD patients had access to WGS, mutations in IRD genes occur at random, and some retinal disease genes may only exist in very few people, adding to the difficulty in finding them. For these reasons, it is useful to take advantage of animal models to work toward a complete atlas of retinal disease genes as well as to test the safety and efficacy of forthcoming cutting-edge therapies.

Rodent Models

The mouse has been used as a very powerful model of mammalian genetics for the past several decades. Mice have roughly ~25,000 protein coding genes, similar to the 19000 protein coding genes in the human genome.[iii] The relative similarity in the number of genes and also the genetic orthologues between species make mice a reasonable model system to unravel the genetic underpinnings of mammalian biology. The size of mice being small, and their lifespan being relatively manageable at roughly two years, along with relatively similar organogenesis and developmental biology are additional features that make them an attractive model system.

Spontaneous models of genetic disease, including inherited retinal diseases, have been identified through observations of and selecting breeding for desired traits. Over the decades many mice with spontaneous retinal phenotypes have been identified. These were named numerically according to the simple convention retinal degeneration 1, 2, 3 (or *rd1, rd2, rd3*) and so on. With due passage of time, additional studies have been able to link the observed traits, retinal degenerations, with causative single gene mutations.

In addition to spontaneously occurring traits such as inherited retinal degeneration, the technology to intentionally target and delete genes of interest was developed and has been pursued vigorously in the last decades of the 20th century. These so called genetic ‘knockout’ mice have broadened our understanding of the requirements of each gene in the mouse genome.

Human inherited retinal diseases have good mouse models useful for answering important biological questions in addition to testing therapeutic strategies. Leber congenital amurosis (LCA) is a devastating photoreceptor degeneration that presents in infancy and results in severe retinal blindness from a very early age. LCA phenotypes in humans differ from one another in some details, but have in common a severely reduced ERG, nystagmus, and oculo-digital reflex. Some mouse models of LCA include Rpe65−/−, Rpe65−/−:Gnat1−/−, Lrat−/−, Lrat−/−:Gnat1−/−, Rdh12−/−, Gc1−/−, Cep290−/−, Crx−/−, Aipl1−/− among others.[4,5,6,7,8,9,10,11,12,13]

Retinitis pigmentosa (RP) is a rod-cone dystrophy that is the most common inherited retinal disease in people. Its clinical features include nyctalopia, loss of peripheral vision,

peripheral bone spicule hyperpigmentation, pallor of the optic nerve, retinal vascular attenuation, preservation of central visual acuity and eventual severe vision loss. RP models in mice include Rgr−/−, Rhodopsin−/−, Rho-P23H, T17M, and Pde6 mutants.[14,15,16,17].

Congenital stationary night blindness (CSNB) is a rod pathway disorder that leads to loss of rod-mediated transmission. Nyctalopia is the main symptom. Nystagmus is present. In general, rod photoreceptors are able to survive rather than degenerate, which can preserve a normal retinal fundus appearance, although there are forms of CSNB with abnormal retinal findings, such as fundus albipunctatus and Oguchi disease. Mouse models of CSNB include Gnat1−/−, Arr−/−, Grk1−/−.[18,19,20].

Stargardt disease is the most common inherited maculopathy and an important cause of vision loss. Stargardt disease is associated with mutations of the ABCA4 gene, which codes for a membrane protein important for exporting the toxic visual cycle metabolite all-trans retinaldehyde out of the photoreceptor. Its malfunction leads to formation of yellow flecks due to accumulation of bis-retinoid N-retinyl-N-retinylidene ethanolamine (A2E), a major component of lipofuscin in the macula and eventually macular RPE atrophy. Abca4 knockout mice accumulate A2E and have some late onset and slowly progressive rod cells loss.[21] However, these mice lack fundus flecks, RPE atrophy, and since mice lack a macula, only partially recapitulate the human disease. The absence of Abca4 in the context of Rdh knockout (Abca4−/−:Rdh−/−) leads to light-induced photoreceptor death and more progressive rod cell loss in addition to A2E accumulation.[22]

Knockout mice have been so valuable to the understanding of mammalian genetics that a worldwide effort has been undertaken to create a library of single-gene deletion mice in an unbiased fashion. The International Mouse Phenotyping Consortium (IMPC) is a group of mouse clinics across the world that have taken on this task. Since 2007 the IMPC has created and phenotyped ~7000 single gene knockout mice resulting in numerous publications. The phenotyping data are made available publicly (www.impc.org). All phenotyping is harmonized between testing centers. An interim analysis of mice with ocular phenotypes has been published.[23] Important to this subject matter is that the genetic background used for IMPC knockouts is the C57BL/6N inbred strain. This strain has been shown to be homozygous the rd8 mutation in the Crb1 cell polarity gene resulting in a mildly progressive variably penetrant retinal degeneration (Figure 1).[24] The C57BL/6N strain has background abnormalities in several parts of the eye, some of which may not be related to the rd8 mutation.[25] The presence of the rd8 mutation in the genetic background is a confounding issue that must be taken into account when determining the genetic relevance of IMPC mice determined to have abnormal retinal morphology (Figure 1). On one hand, the presence of rd8 complicates the interpretation of retinal phenotyping such that all IMPC mice are in a sense double knockouts. On the other hand, the presence of the rd8 mutation in the background of the mice creates a sensitized screen for retinal phenotypes which may reveal genes important for retinal development and biology that may not have been picked up except for the presence of the underlying rd8 mutation. In any case, the most accurate understanding of the genetic relevance of IMPC knockout mice with retinal abnormalities requires breeding mice with the targeted deletion of interest off of the rd8 background.

The utility of mouse models of inherited retinal disease cannot be overstated. Mouse models have been used for pre-clinical trials of retinal gene therapy[26] for many single-gene disorders. These include rescues of mice with mutations in ABCA4,[27] RS1,[28,29] CNGB3,[30] CNGA3,[31,32,33] PDE6B,[34,35] PDE6A,[36] RPE65,[37,38] among others. Mice have been used for major apparent advances in cell transplantation,[39] some of which have opened the field of material exchange/transfer.[40,41] Finally, mutant mouse models have been very useful for regenerative strategies to induce endogenous retinal cells to re-enter the cell cycle and replenish lost cells.[42,43,44] While it is not clear if cell transplantation or in situ cell regeneration will ultimately best serve to restore vision in humans with end stage retinal degenerations, it is likely the foundational experiments will be performed first in rodent models.

Despite the many advantages of using mice to study inherited retinal disease, there are major limitations to research programs limited to murine models. First, although there are more genetic similarities than differences between mouse and human, the dissimilarities are significant enough that several notable knockout models have failed to completely recapitulate disease phenotypes in mice, including models for Stargardt disease,[45] Usher syndrome,[46] and less common photoreceptor dystrophies such as Jalili syndrome.[47] Perhaps the most notable limitation is the anatomical difference in the posterior retina as mice lack a high acuity center (macula). The absence of a macula makes mice an inadequate model for macular diseases and cone disorders. In conjunction with the much shorter lifespan compared to humans, and the lack of a macula, there are no ideal mouse models of age-related macular degeneration (AMD), perhaps the most common cause of retinal blindness in the America. While some mouse models of various features of AMD have been described, none fully recapitulate the disease process or phenotype.[48,49,50] These limitations among others necessitate the use of large animal models of inherited retinal disease.

Dog and Cat Models

Progressive retinal atrophy (PRA) is a group of degenerative diseases of the retina that occur in dogs and cats. The underlying causes are genetically heterogenous. Many models of PRA have been characterized in dogs [51] and some in cats as well. Several modes of inheritance have been observed including autosomal recessive, autosomal dominant, and X-linked transmission. Several breeds of felines have been observed to suffer from an autosomal recessive form of PRA designated as rdAc. This form of PRA has been linked to a mutation in the feline Cep290 gene.[52,53,54]

While rdAC cats eventually go blind due to their disease, the retinal degeneration is usually relatively late onset and slowly progressing. Humans with mutations in CEP290 have a variable phenotype based on the severity of the mutation. Some mutations are associated with disease limited to the eyes in the form of retinal degeneration such as Leber Congenital Amaurosis, a severe blinding disease of childhood, accounting for up to 20% of human cases.[55,56] Cince CEP290 is a ciliary protein, it should not be surprising that some other mutations can result in multi-system features in the spectrum of Meckel[57,58], Joubert[59,60,61], and Senior-Løken syndromes.[62,63] The findings in the rdAc cats recapitulate some of those

seen in humans with LCA, specifically photoreceptor degeneration with loss of the ellipsoid zone (aka IS/OS junction), which initially spares the feline area centralis.[64]

At least one other feline model of PRA exists, the rod-cone dysplasia (Crx^{Rdy}) cat. These cats have a spontaneous 1-bp deletion mutation in the cone-rod homeobox (CRX) gene resulting in a frameshift mutation.[65] A premature stop codon results in a truncated message lacking the terminal 114 amino acids. Similar mutations in human patients lead to a clinical diagnosis of LCA.[66] This leads to a dominantly inherited severe retinal degeneration.[67,68,69,70,71] Retinal degenerations associated with CRX in humans can result in early severe vision loss (LCA) as well as other more slowly progressive photoreceptor diseases, including retinitis pigmentosa, cone-rod dystrophy, and macular dystrophy.[72,73] They are dominantly inherited, similar to the feline model. These cats have a non-recordable ERG at birth, delayed development of rod responses which are markedly reduced and lost completely by 20 weeks postnatal age. Development of photoreceptor outer segments is incomplete. Photoreceptor degeneration ensues starting in the area centralis, consistent with a cone-rod pattern of degeneration.[74] These kittens are therefore a good large animal model for CRX-associated LCA.

Another feline model of LCA is the AIPL1 Persian cat.[75] This gene is associated with LCA in humans accounting for less than 10% of recessive LCA in human populations.[76] AIPL1 is a photoreceptor protein responsible for folding and chaperoning phosphodiesterase (PDE6) to the outer segment.[77,78,79,80,81] The mutation in these cats is a C>T resulting in an early stop codon. A truncated protein is produced which is not functional.[82] In these cats, there is very early and severely progressive photoreceptor loss and retinal degeneration prior to adulthood leading to early blindness, making them a useful model of AIPL1-associated LCA.

Recently a feline model of RDH5-associated retinopathy has been described.[83] This enzyme catalyzes 11-cis retinol to 11-cis retinaldehyde in the retinal pigmented epithelium (RPE) to be transported to the photoreceptor outer segment as part of the visual cycle. Mutations in RDH5 are associated with fundus albipunctatus in humans.[84] In addition to the diffuse spots seen in this fundus, cause cone dysfunction[85] and macular dystrophy can be features of the phenotype.[86,87] The RDH5 cat shows a delayed photoreceptor recovery after light exposure, similar to the human ERG observation and also undergoes atrophy of the area centralis.

While there are only a handful of retinopathies characterized in cats, dog models of retinal degeneration abound. At least 31 single gene disorders causing retinal disease in dogs have been identified due to several groups who have dedicated their entire careers to focusing on canine models of PRA. Their work has culminated in the generation of the first FDA-approved gene therapy in all of medicine for RPE65, a gene responsible for LCA and retinitis pigmentosa.

Examples of canines with PRA have been identified affecting phototransduction, the visual cycle, channelopathies, ciliopathies, synaptogenesis, retinal development, as well as structural and metabolic dysregulation. Dogs with mutations in Rhodopsin, rod-specific Phosphodiesterase (PDE6A, PDE6B), and SAG have been reported. The PDE6A dog has a

frameshift mutation leading to an early stop codon and no measurable protein.[88,89] Of note, no PDE6B protein is detectable in the retina of these animals, indicating a requirement for the PDE6A subunit for stable production of the remaining components of this enzyme on rods. Absence of phosphodiesterase activity leads to an accumulation of cGMP with chronic influx of calcium into the photoreceptor outer segment and subsequent cell death.[90,91] Retinal degenerative changes are clearly detected by indirect ophthalmoscopy and retinal thinning is seen by OCT (Figure 3). AAV-mediated gene replacement was able to restore visual function in these animals.[92,93] A similar phenotype is seen in the PDE6B mutation originally identified in Irish Setters.[94] Absence of PDE6B does not abolish PDE6A protein, indicating a requirement of the latter for production of the former, but not vice versa. The PDE6B protein is absent due to an early stop codon in this nonsense mutation affecting the C-terminal domain, leading to elevated cGMP concentrations. These animals have rods that fail to elaborate functional outer segments. Gene therapy is able to stop disease progression in these animals.[95]

Canines with visual cycle mutations in RPE65 and ABCA4 have been published. ABCA4 is famously associated with Stargardt maculopathy in humans but can also cause cone-dystrophy and RP. Labrador retrievers can harbor a single base pair deletion resulting in a frameshift in this gene.[96] These dogs accumulate lipofuscin in the outer retina and some older animals have abnormalities in retinal function with decreased numbers of photoreceptors. Cyclic nucleotide gated channel subunits involved in rod (CNGA1, CNGB1) and cone (CNGA3, CNGB3) phototransduction also exist. A canine model of BEST1-associated retinopathy has been described. The RPE65 dog model is a model of LCA which has resulted in the development of an FDA-approved viral mediated gene therapy. The gene therapy product resulted in slowed loss of photoreceptors, restoration of the ERG, and improvement in visual functioning.[97,98,99,100] Humans with disease associated with RPE65 have shown overall beneficial responses, but perhaps not quite as robust or durable as that seen in the canines afflicted with this disease likely due to species differences in the biology of isomerase activity in RPE cells.[101].

Based on Gene Ontology[102], SYSCILIA Gold Standard[103], and CiliaCarta[104], nearly one thousand proteins are associated with the cilium. It is postulated that mutation in any of these could potentially cause retinal disease, since the photoreceptor outer segment is a modified primary cilium. The number of genes responsible for ciliopathies continues to grow as understanding of this important cellular organelle deepens. Many dogs with ciliopathies have been identified. These include BBS4, c2orf71, CCDC66, FAM161A, NPHP4, NPHP5, RPGR, RGRIP1, and TTC8. The primary cilium is a cellular organelle that exists in many human cell types and serves a sensory function to detect soluble signaling molecules and growth factors. Primary cilia are important in developmental biology and normal cellular functioning. A cilium is composed of a long axoneme with 9 microtubule doublets in parallel that run along its length. The axoneme is anchored to the cell by a basal body composed of microtubule triplets related to centrioles BBS4 is part of the BBSome, composed of seven highly conserved BBS proteins and is involves in intraflagellar transport (IFT) along the axoneme. TTC8 is associated with BS4. CEP290 and c2orf71 are also involved in IFT regulation. CCDC66 is a centriolar settelite protein required for ciliogenesis. FAM161A is associated with the basal body. NPHP4 and NPHP5 are part of

the NPHP module, which establishes basal body/transition zone and ciliary gate function during ciliogenesis. RPGR and RGRIP1 are associated with the NPHP module (see Chen et al. 2020 for review).[105] Canines with mutations in the above genes have photoreceptor degeneration due to failure of ciliary development or maintenance.

Mutations in genes with other functions can also lead to dogs with PRA, including STCK38L, which is required for retinal development. LRIT3 dogs are a model of congenital stationary night blindness in humans due to faulty photoreceptor synapses with bipolar cells. MERTK mutations disrupting RPE cell phagocytosis of photoreceptor outer segments have been reported. ADAM9, PRCD, RD3, NECAP1, PPT1, and SLC2A3 genes also have dog models.

Pig Models

Several transgenic pigs have been engineered as models of retinitis pigmentosa secondary to mutations in rhodopsin. The advantages of the pig as a model organism for genetic disease includes the similarities between the human genome and other mammals, in addition to a large eye that is similar to the human in overall size. The porcine eye has an axial length of 23.9 ± 0.08 mm,[106] very similar to humans. In addition, pig eyes are amendable to vitrectomy, gene therapy, and other surgical manipulations in pre-clinical studies. Pigs have a holangiotic retinal vascular system[107] similar to humans and have a cone-rich area centralis.[108,109] Furthermore, they have a similar scleral thickness, which is relevant to their use for surgical innovation. Importantly, like humans they lack a tapetum, which is a fundamental dissimilarity between many large-eyed mammals and humans. Compared to non-human primates, pigs have a shorter gestational age (114 days) and a larger number of offspring per pregnancy with litters of 8-12 in size making translational experiments scalable.

Pigs have been used to produce transgenic models of rhodopsin-associated RP based on mutations in the RHO gene in human populations. The most well-known and common of these RHO mutations in the Pro23His mutation.[110] This mutation is common in human populations of dominant RP. The transgenic Pro23His pig has been used to study cone photoreceptor death secondary to rod loss. The cone photoreceptors in this animal were able to be reactivated in response to subretinal glucose administration, suggesting they are metabolically dormant prior to undergoing cell death in response to rod degeneration.[111] In addition, Pro347Ser[112] and Pro 347Leu[113] transgenic animals have been produced. Work in these models has contributed important knowledge of cell death pathways and the role of oxidative stress to photoreceptor loss in RP.[114] There are two porcine transgenic model of Stargardt retinopathy with truncation mutations in ELOVL4 identified in humans.[115] These animals have disorganized photoreceptors and reduced ERG signals. Spontaneous examples of retinal disease in pigs have not been published to date.

Monkey Models

An NHP model of Bardet-Biedl syndrome has been characterized recently.[116] These monkeys have a spontaneous mutation in the BBS7 gene deletion resulting in an early stop

codon and truncated protein product that is non-functional. As part of the BBSome, BBS7 is required for ciliogenesis and regulation of IFT in photoreceptors and in other ciliated cells. These monkeys not only had retinal degeneration affecting the central retina more than the peripheral regions, but also systemic abnormalities. Specifically, they had small brain size, kidney disease, and small gonads. This constellation of systemic findings is consistent with humans with Bardet-Biedl syndrome and this model may facilitate improved understanding of the underlying biology of this disorder and potential therapeutic strategies.

Another syndromic form of retinal degeneration, Batten disease, associated with CLN7 has been described in Japanese macaques.[117] These animals are homozygous for a frameshift mutation in CLN7 resulting in a null allele. The homozygotes have significant neurological manifestations including vision impairment due to retinal disease. In addition, they have coordination defects, tremor, ataxia, and loss of balance. The retina has reduced thickness and abnormal retinal function. They also have atrophy of the cerebral hemispheres, cerebellum, and loss of white matter with reactive gliosis. The findings closely recapitulate the breadth and severity of Batten disease in humans and may help in evaluating therapeutic strategies for this devastating condition.

Non-syndromic retinal degenerations in NHPs are rare. A family of cynomolgus macaques has been identified with retinitis pigmentosa.[118] The two affected animals in this pedigree had cystoid macular edema and peripheral bone-spicule hyperpigmentation. Both animals had an essentially non-recordable full-field ERG with loss of photoreceptors on the OCT outside of the macula. Whole genome sequencing was pursued but no genetic cause for the suspected recessive inheritance pattern could be identified.

Bilateral macular dystrophy was identified in a single rhesus macaque in Germany.[119] Detailed functional and structural characterization was performed using advanced retinal imaging methods, including fluorescein angiography, indocyanine green angiography, and SD-OCT. Electroretinography with both full-field and multifocal modalities were performed and eyes were taken for histology. The macular lesion in the retina was markedly atrophic without large areas of RPE involvement. The lesions were symmetric between both eyes suggesting a possible underlying genetic etiology, though environmental factors cannot be excluded. Genetic analysis was not performed.

Idiopathic bilateral optic atrophy (IBOA) has been reported in rhesus macaques which causes axonal loss and gliosis limited to the temporal optic nerve fibers.[120] The papillomacular bundle is the primary area affected in these monkeys. There were reductions in the high-frequency components of the multifocal ERG while the other parts of the ERG attributed to photoreceptors and inner nuclear layer function were unaffected. The loss of the retinal nerve fiber layer correlated to the functional loss detected in the high-frequency MF ERG components. The underlying presumed genetic etiology for IBOA in these animals has yet to be identified.

Recently our group at UC Davis has identified four animals with behavior suspicious for decreased visual functioning that were ultimately attributed to homozygous mutation of the PDE6C gene in cone photoreceptors.[121] Two of the four animals were known to be cousins,

and later the other two were found to be related on larger pedigree linked to a common founder who was ultimately proven to be a heterozygous carrier of the same mutation, and also an alpha male in the colony with many progeny that ultimately led to the birth of the four homozygotes identified by the veterinary staff members with decreased vision. These animals had a bullseye maculopathy visible on fluorescein angiography, subtle pigmentary changes on color fundus photography, and thinning of the foveal center with disruption of the cone outer segment tips (Figure 4). Genetic analysis revealed a single nucleotide shift that resulted in an arginine to glutamine change in the amino acid sequence (R565Q). The arginine is in the catalytic domain of the cone phosphodiesterase enzyme and is conserved in the amino acid sequence across many vertebrates including fish, birds, mice, NHP, and humans. The mutation results in a stable protein product but the enzyme was found to have no catalytic function on biochemical testing. The characteristics of the mutant animals were most similar to a severe cone disorder similar to achromatopsia in humans, though the clinical overlap is not exact in every respect. These animals will be useful for preclinical gene therapy trials and potentially for other advanced therapeutic studies.

Conclusion

Animal models of single gene disorders are indispensable. They provide critical insights to the pathophysiology of disease that could never be otherwise known due to the scarcity of human tissues. Furthermore, the very same animal models that lend us a better understanding of the role of various genes and their protein products in retinal function and degenerative states also themselves serve as an ideal preclinical venue for testing therapeutic strategies. Due to the relative ease of manipulation and abundance of available tools, mouse models often serve as the initial site of biologic inquiry. However, due to significant differences in eye size, larger animal models can be very beneficial to advance gene therapies. Genetic differences between rodents and humans, notably in the case of some Usher syndrome models which generally develop hearing loss without retinopathy, demonstrate that murine models can be inadequate to model human disease. Furthermore, especially due to the absence of a macula in rodents, disease models for cone disorders and macular dystrophies and degenerations may benefit from nonhuman primate models that share this area of retinal specialization.

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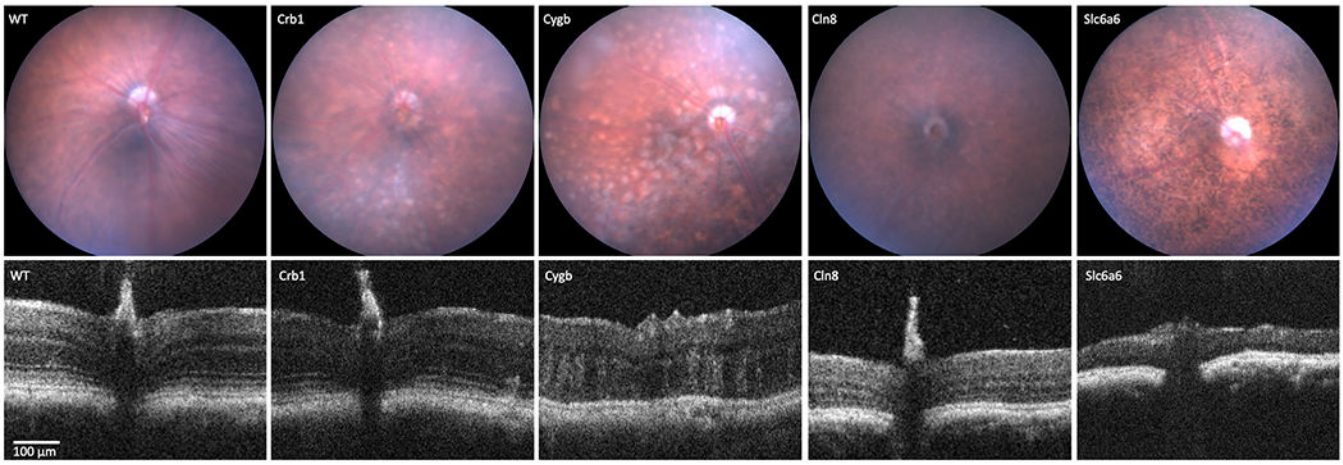

Figure 1.

Mouse models of inherited retinal disease. Fundus photos (top row) and OCT through the optic nerve (bottom row) at age 4 months postnatal are shown with wild type (WT) control mice in the first (left) column. Crb1 mutant (rd8) mice have round white dysplastic lesions mostly in the inferior retina that correspond to outer retinal hyperreflective foci on OCT and pseudorosettes of photoreceptors on hisology (not shown). Deletion of Cygb in the context of rd8 mutation exacerbates the extent and severity of the outer retinal pseudorosette dysplastic lesions. Cln8 deletion results in retinal vasculature attenuation on fundus photos and retinal thinning due to photoreceptor loss on OCT. Deletion of Slc6a6 (Taurine receptor) results in diffuse foci of hyperpigmentation and optic nerve pallor on fundus photos and severe retinal thinning and disorganization on OCT.

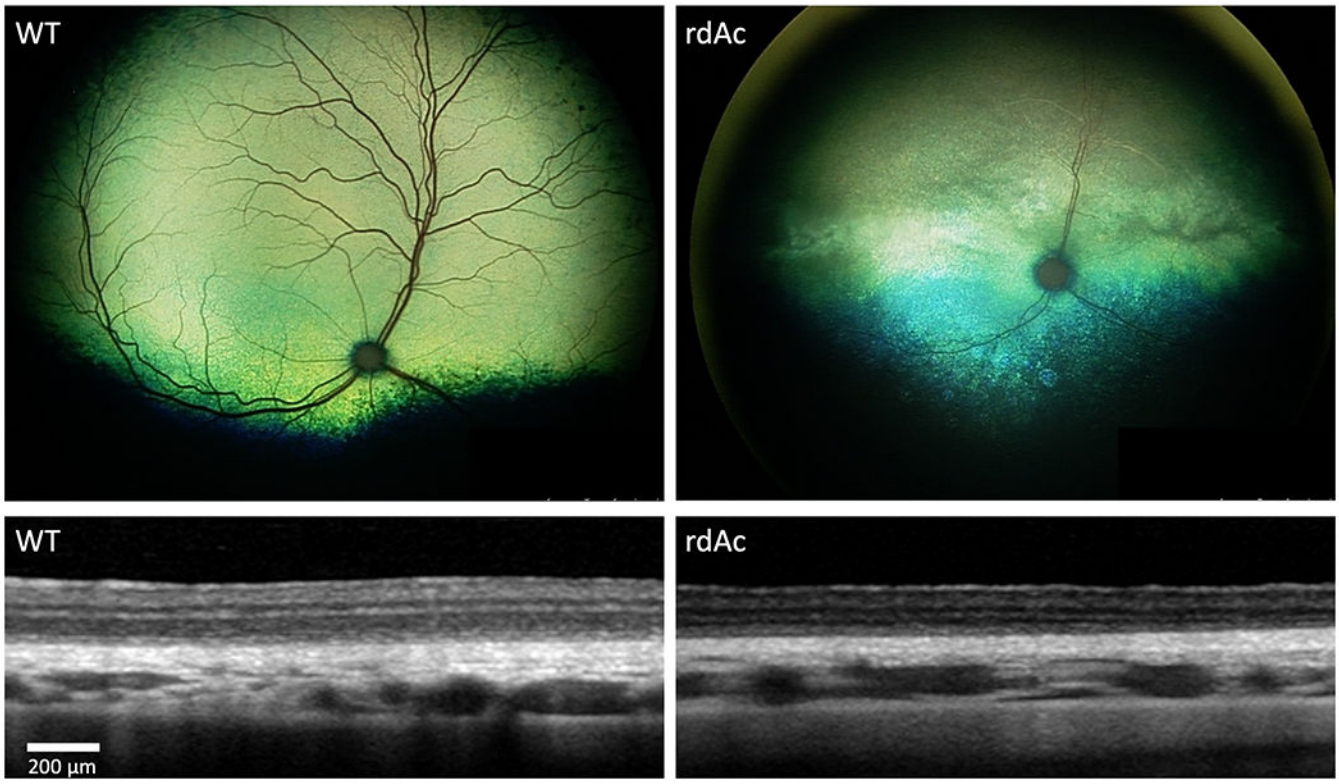

Figure 2.

CEP290 associated retinopathy in the rdAc feline model. Compared to wild type control cats (left column), the rdAc fundus (top right) shows loss of the tapetal reflex in the superior retina, pigmentary changes, retinal vascular attenuation, and involvement of the area centralis by age 8 years. Compared to the control OCT (bottom left), the rdAc animals have retinal thinning with thinning of the outer nuclear layer secondary to photoreceptor loss (bottom right).

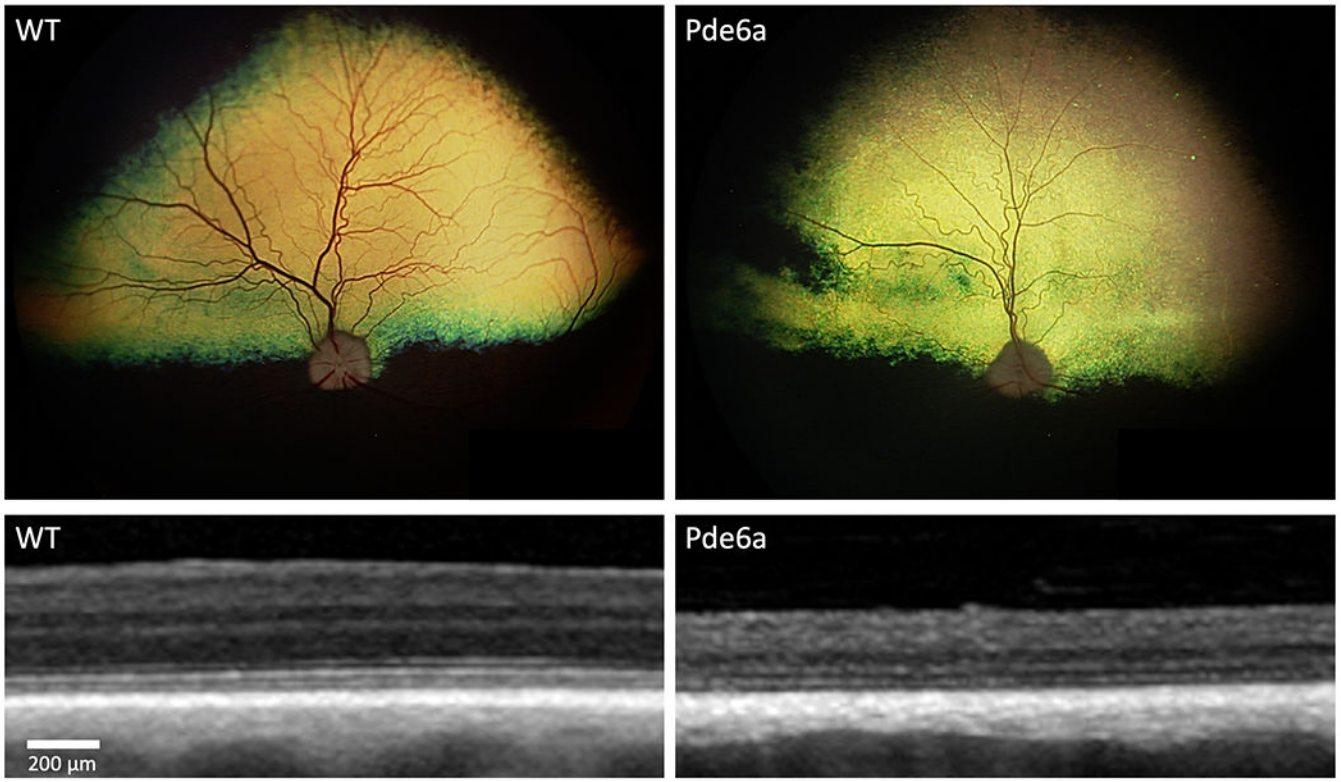

Figure 3.

Pde6a associated retinopathy in canines. Compared to wild type animals (left column), the tapetal reflex is decreased in the superior retina of the Pde6a homozygotes by age 7 months (right column). Fundus photos show pigmentary changes and retinal vascular attenuation consistent with retinal degeneration in Pde6a animals. The OCT of Pde6a dogs (lower right) demonstrates retinal thinning and loss of outer retinal lamination compared to wild type (lower left), consistent with photoreceptor loss.

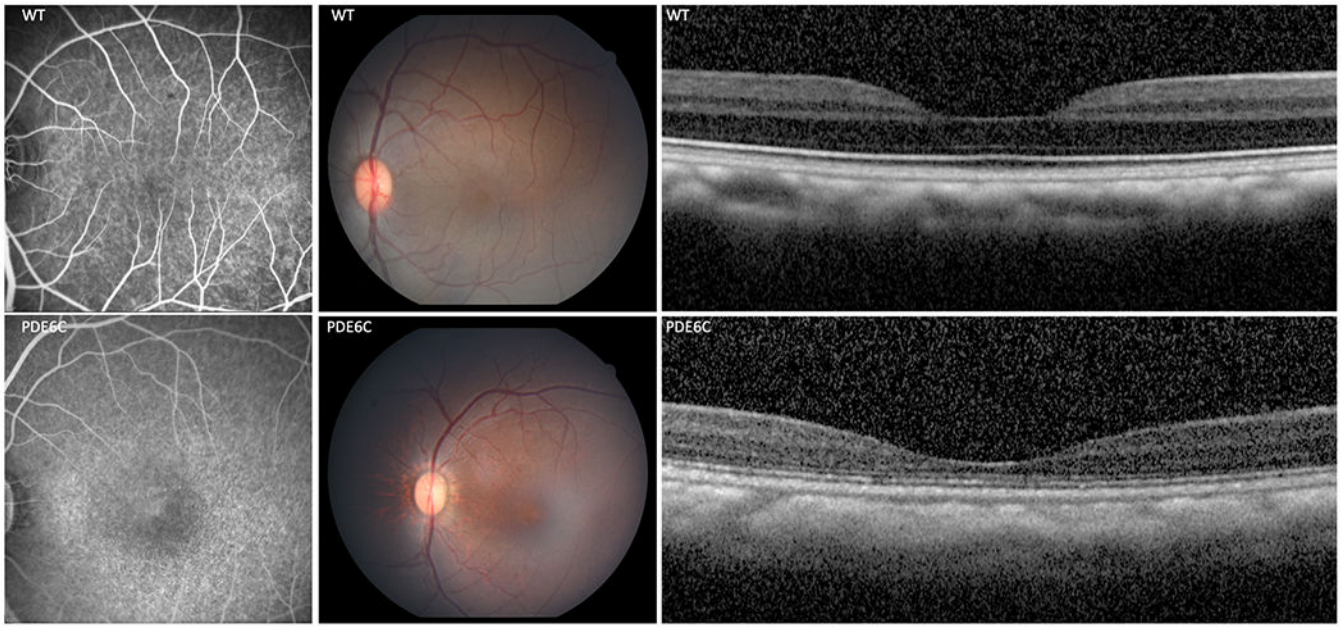

Figure 4.

PDE6C associated retinopathy in non-human primates. Compared to wild type controls (top row), rhesus macaques homozygous for a mutation in PDE6C (bottom row) have a subtle bullseye maculopathy visible on fluorescein angiography by age 13 years (left column). Subtle macular pigmentary changes are seen on fundus photography (middle column). Retinal thinning and subtle discontinuity of the ellipsoid zone (aka IS/OS junction) are seen in the foveal center (right column). The cone-mediated response is completely absent on full-field electroretinography from the earliest time-point measured, 6 months post-natal (not shown). The phenotype of PDE6C animals most closely resembles achromatopsia in humans.