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Genetic models of retinal degeneration and targets for gene therapy

Review Article

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Abbreviations: adeno-associated virus, (AAV); age-related macular degeneration, (AMD); Ames waltzer, (av); amyloid beta, (Aβ); aryl-hydrocarbon interacting protein-like 1, (AIPL1); Bardet-Biedl syndrome, (BBS); Caribbean Primate Research Center, (CPRC); cathepsin D, (CatD); C-C chemokine receptor-2, (Ccr2); centrosomal protein 290, (CEP290); ceruloplasmin, (Cp); choroidal neovascularization, (CNV); complement factor H, (CFH); cone degeneration, (cd); cone photoreceptor function loss, (cpfl); cone-rod dystrophy, (cord1); cone-rod homeobox, (CRX); Congenital stationary night blindness, (CSNB); crumb's homolog 1, (CRB1); cyclic guanosine monophosphate phosphodiesterase, (cGMP PDE); cyclic nucleotide gated channel α3, (CNGA3); cyclic nucleotide gated channel β3, (CNGB3); cyclic nucleotide-gated, (CNG); doublecortin, (DCX); electroretinograms, (ERG); guanine nucleotide binding protein, (GNAT2); guanylate cyclase, (GC); guanylate cyclase-activating proteins, (GCAPs); hephaestin, (Heph); hypoxia inducible factor-1α, (HIF-1α); interphotoreceptor retinoid binding-protein (IRBP); Leber Congenital Amaurosis, (LCA); low density lipoprotein, (LDL); luteinizing hormone beta subunit (LHbeta); McKusick-Kaufman syndrome, (MKS); monogenic audiogenic seizure-susceptible gene, (MASS1); Myosin VIIa, (MYO7A); neprilysin, (NEP); N-retinylidine-phosphatidylethanolamine, (N-RPE); photoreceptor-specific guanylate cyclase, (GUCY2D); pigment epithelium-derived growth factor, (PEDF); prokineticin 1, (hPK1); proline at position 27, (P27L); retinal degeneration 3, (rd3); retinal degeneration 5, (rd5); retinal degeneration slow, (rds); retinal degeneration, (rd); retinal dystrophy, (rdy); retinal pigment epithelium, (RPE); retinitis pigmentosa GTPase regulator, (RPGR); Retinitis pigmentosa, (RP); rhodopsin, (Rho); rod-cone dysplasia 3, (rcd3); rod-cone dysplasia, (rcd1); Royal College of Surgeons, (RCS); Sorsby fundus dystrophy, (SFD); superoxide dismutase, (SOD1); simian virus 40 T antigen (SV40 Tag); tissue inhibitor of metalloproteinases-3, (Timp3); tubby, (tub); tubby-like protein 1, (TULP1); Usher syndrome, (USH); valine at position 20, (V20G); vascular endothelial growth factor, (VEGF); very large G-protein couple receptor family, (VLGR1);very low density lipoprotein, (VLDL); waltzer, (v)

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Summary

Studies utilizing animal models in combination with progress in the field of molecular genetics have improved our understanding of pathways leading to retinal degenerations. As a result, it has become clear that genes are involved in many processes that are responsible for the symptomatology seen in these conditions. However, it is still a mystery how certain genetic defects can cause a myriad of retinal degenerations while others defects, often in the same genes, lead to much more benign conditions such as stationary night blindness. As future research uncovers new details about specific genetic defects and the discovery of more accurate animal models, we can hopefully develop gene therapeutic strategies that will one day prevent, treat, and even cure these blinding and debilitating diseases.

I. Introduction

Retinal degenerative diseases are the leading cause of irreversible blindness in western countries today. In contrast, our knowledge of the underlying pathophysiology and hence, targets for therapeutic intervention, are limited. While many retinal degenerations are believed to have a multifactorial etiology, we now know that there is a genetic component that is at least partially responsible for the clinical manifestations seen in many of these diseases, such as

retinitis pigmentosa and age-related macular degeneration (AMD). As a result, the development of accurate and reproducible disease models is critical for identifying the genes and underlying mechanisms by which retinal diseases occur. Most current models of retinal degenerative disease are the result of naturally occurring mutations in humans or animals, particularly rodents. However, technological advances have led to significant developments in genetic engineering, which have allowed researchers to manipulate the expression of genes involved in both retinal disease and normal retinal function (Tsang et al, 1996, 1998, 2007). In this review, we will summarize the most significant inherited retinal diseases and the available animal models currently used to study them.

II. Degenerations of the macula

Macular degeneration is a heterogeneous group of diseases that mainly affect the macular region of the retina. As a result, the primary clinical finding is a defect in central vision. In contrast to global retinal diseases and cone-predominant degenerations, normal full-field electroretinograms (ERG) and peripheral visual fields are seen in macular dystrophies. Pathologically, they are characterized by atrophy and degeneration of the retinal pigment epithelium (RPE) and photoreceptors. As a group, macular degenerations are the leading cause of irreversible blindness in the general population, particularly among the elderly and in the western world.

A. Best disease

Best Disease is a congenital disease of autosomal dominant inheritance that affects the central retina. Also known as vitelliform macular dystrophy, its name is derived from the appearance of the classic vitelliform, or "egg yolk" lesion seen in the macula. This characteristic finding is the result of excess lipofuscin in the RPE cells across the fundus as well as degenerating pigment epithelial cells located between the RPE of the fovea and Bruch's membrane. These findings are also accompanied by the loss of foveal photoreceptors (O'Gorman et al, 1988). Best Disease is diagnosed by a reduced Arden ratio on the electrooculogram. It is now known that a mutation in the VMD2 gene on chromosome 11q13 is responsible for Best Disease (Petrukhin et al, 1998). VMD2 encodes a protein called bestrophin, which acts as a chloride channel in the basolateral membrane of the RPE (Sun et al, 2002). Currently, VMD2 is not thought to be a major contributer in the etiology of AMD (Allikmets et al, 1999; Kramer et al, 2000; Lotery et al, 2000b).

1. Models of Best disease

Recently, Marmorstein and colleagues reported a rat model of Best Disease using adenovirus gene transfer in wildtype animals to cause overexpression of bestrophin and two bestrophin mutants - bestrophin W93C and bestrophin R218C (Marmorstein et al, 2004). Their study showed that the reduced light peak amplitude that is characteristic of Best Disease is seen to varying degrees in mutants expressing bestrophin W93C and R218C. Though all animals exhibited similar waveforms of the major ERG components (a- and b-wave), diminished amplitudes were seen when compared to controls.

B. Stargardt disease

Unlike the other common macular dystrophies (most of which have a dominant inheritance pattern), Stargardt Disease has an autosomal recessive mode of inheritance. Abnormally high accumulations of lipofuscin in the RPE of patients with Stargardt Disease leads to atrophy and the formation of a "bull's eye"-like lesion on the fundus (**Figure 1**). Yellowish "fishtail" flecks are also seen at the level of the RPE (**Figure 2**) – a phenomenon known as fundus flavimaculatus (Klaver et al, 2003).

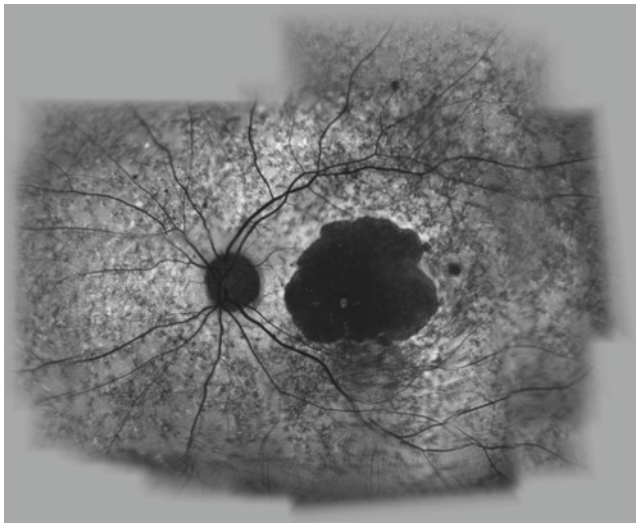

Figure 1. Autofluorescent imaging shows RPE atrophy (hypofluorescent) centrally and A2E related flecks (hyperfluorescent) in an individual with compound heterozygous mutation in the ABCA4 gene.

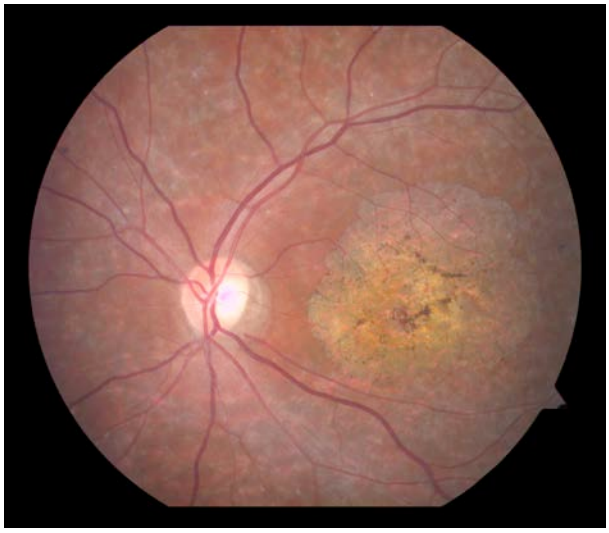

Figure 2. Corresponding fundus photo of Figure 1. Notice the presence of the yellowish "fishtail-like flecks" prominent in macular region to the right of the optic nerve.

Due to the work of Allikmets and colleagues, it is now known that ABCA4, also known as ABCR, is the gene that is responsible for Stargardt disease (Allikmets et al, 1997). ABCA4 encodes a protein called rim, which is a transmembrane protein involved in the transport of vitamin A intermediates, specifically N-retinylidine-phosphatidylethanolamine (N-RPE), to the RPE. As its name suggests, the rim protein is expressed in the rims of photoreceptor disc membranes. Alterations in the normal function of ABCA4 lead to N-RPE accumulation in the outer segments of the photoreceptor discs, which leads to the formation of the lipofuscin component, N-retinylidene-N-retinylethanolamine (A2E). As a result, high levels of lipofuscin accumulate in the RPE, causing the subsequent photoreceptor degeneration seen in Stargardt Disease.

1. Models of Stargardt disease

An Abca4 knockout mouse was developed which has expanded our knowledge of this disease and has identified possible targets for therapeutic intervention (Weng et al, 1999). Mice lacking rim protein develop delayed dark adaptation and increased all-trans-retinaldehyde following light exposure. In addition, there is increased accumulation of both lipofuscin and A2E, the toxic lipofuscin fluorophore, within the RPE cells (Mata et al, 2000; Weng et al, 1999). A2E accumulation eventually causes secondary degeneration of photoreceptors. To date, the $Abca4^{-/-}$ mouse is the only genetic model of recessively inherited Stargardt Disease.

C. Sorsby fundus dystrophy

Sorsby fundus dystrophy (SFD) is an autosomal dominant condition that causes visual loss in affected individuals at approximately 40 years of age. It has been linked to a mutation in the tissue inhibitor of metalloproteinases-3 (TIMP3) gene, which encodes a TIMP3 protein that inhibits the action of matrix metalloproteinases (Weber et al, 1994). Starting around the fourth decade of life, affected patients present with problems transitioning between light and dark followed by central vision abnormalities and late loss of peripheral vision (Sorsby et al, 1949). Clinically, the formation of drusen is accompanied by choroidal neovascularization that grows into the subretinal space through a thickened Bruch's membrane (Polkinghorne et al, 1989). As a result, SFD has garnered much interest because of its clinical similarities to AMD.

1. Models of Sorsby fundus dystrophy

To date, only one model of SFD has been developed. Weber and colleagues developed a knock-in mouse carrying the Ser156Cys mutation in the Timp3 gene using site-directed mutagenesis and homologous recombination in embryonic stem cells (Weber et al, 2002). After eight months, abnormal morphology was seen in both Bruch's membrane and the RPE. Scotopic and photopic ERGs were normal during the lifespan of affected $Timp3^{S156C/S156C}$ mice. Neovascularization was not seen in these mice.

D. Stargardt-like macular dystrophy

An autosomal dominant variant of Stargardt disease is known as Stargardt-like macular dystrophy. Much like classic Stargardt disease, electrophysiologic findings can vary but tend to be fairly normal in this condition. In contrast, the appearance of a "dark choroid" that is commonly seen on fluorescein angiography in recessive Stargardt disease patients is absent in Stargardt-like macular dystrophy (Klaver et al, 2003). Stargardt-like macular dystrophy is much less common than recessive Stargardt disease, and it was not until 2001 that ELOVL4 was identified as the responsible gene (Zhang et al, 2001b). It is thought that ELOVL4 encodes an enzyme that is highly expressed in photoreceptor cells and is involved in the elongation of very long chain fatty acids, hence its name (Mandal et al, 2004; Zhang et al, 2003b). It has been hypothesized that the ELOVL4 protein contributes to proper photoreceptor function and membrane composition because of its role in the synthesis of polyunsaturated fatty acids of the outer segment (Klaver et al, 2003). Genetic analyses of Stargardt-like macular dystrophy pedigrees have demonstrated that a 5 base-pair (bp) deletion or two 1 bp deletions result in the formation of a truncated ELOVL4 protein that causes macular disease (Bernstein et al, 2001; Zhang et al, 2001b).

1. Models of Stargardt-like macular dystrophy

The identification of ELOVL4 as the responsible gene for Stargardt-like macular dystrophy eventually led to the development of a transgenic mouse model for studying the disease (Karan et al, 2005). The Elovl4 transgenic mouse expresses a mutant form of human ELOVL4 resulting from a 5 bp deletion that produces an accumulation of phagosomes and lipofuscin in the RPE, much like the Abca4 knockout mouse. Photoreceptor degeneration develops and abnormal ERG changes are seen subsequently. As a result, this mouse model exhibits some features of both Stargardt-like macular dystrophy as well as rod-cone dystrophy.

E. Age-related macular degeneration

AMD is the leading cause of visual impairment among the elderly in the United States and other developed countries. As its name suggests, it is relatively localized to the macula, and the prevalence increases with age. The end result is ultimately the progressive deterioration of (fine) central vision. AMD is clinically divided into two types: atrophic (also known as dry or nonexudative) and exudative (wet). Atrophic AMD, which accounts for the vast majority of all cases, is characterized by deposits called "drusen" between the RPE and Bruch's membrane (**Figure 3**). The accumulation of A2E and its isomers along with subsequent RPE death leads to secondary degeneration of photoreceptors (Kim et al, 2004). Eventually, the retina thins and visual impairment occurs. In contrast, exudative AMD is characterized by choroidal neovascularization (CNV). Rapid visual impairment occurs when newly formed vessels leak into the subretinal space and damage the retina. Though only

about 10% of patients develop exudative AMD, it accounts for the vast majority of cases of severe visual loss. While there is some debate as to whether both forms are related or represent separate disease processes, polymorphisms in complement factor H (CFH) have been linked to both types suggesting an association between the two forms (Chen et al, 2006; Fuse et al, 2006).

AMD is thought to have a multifactorial etiology in which both genetic and environmental risk factors (e.g. smoking and diet) contribute to the development of disease. One of the main hurdles in studying AMD has been the lack of precise animal models to study the disease and to elucidate the genetic components involved. While association studies have clearly implicated the role of genetics in the development of AMD, elucidation of a clear-cut causal gene(s) has been difficult (Klaver et al, 1998; Hammond et al, 2002). Fundus photos comparing a patient with exudative AMD with a normal fundus are shown in **Figure 4A** and **B**.

1. Rodent models of age-related macular degeneration

Rodents, specifically mice, are currently the primary species used to study AMD. Though rodents lack a macula, they offer several advantages for studying retinal disease in spite of this deficit. They are cheap and easy to handle. As a result, they can be studied in high numbers, while their relatively short lifespan allows for timely and efficient study of diseases of the elderly, such as AMD. Perhaps even more significant is the fact that rod-cone photoreceptor interactions with the retinal pigment epithelium are conserved between humans and mice. In addition, a wide variety of hereditary retinal degenerations occur in mice, and genetic manipulation is fairly simple, reproducible, and well-established in the medical literature. More importantly, many of the disease genes in mice possess a corresponding human equivalent.

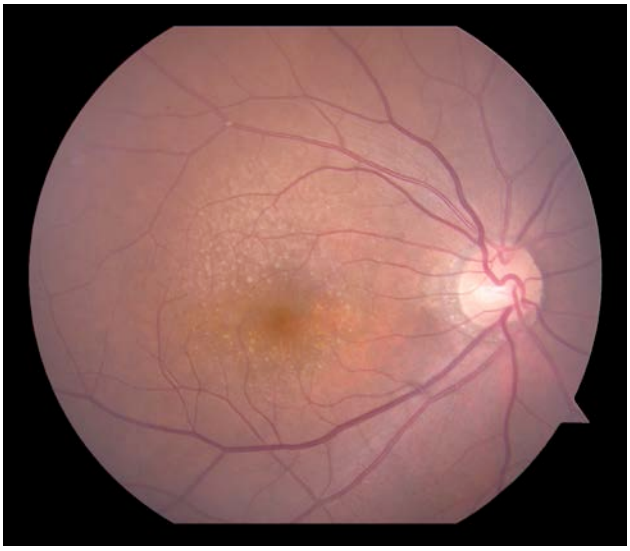

Figure 3. Fundus photo of a patient with atrophic macular degeneration. Drusen can be seen in the area of the macula.

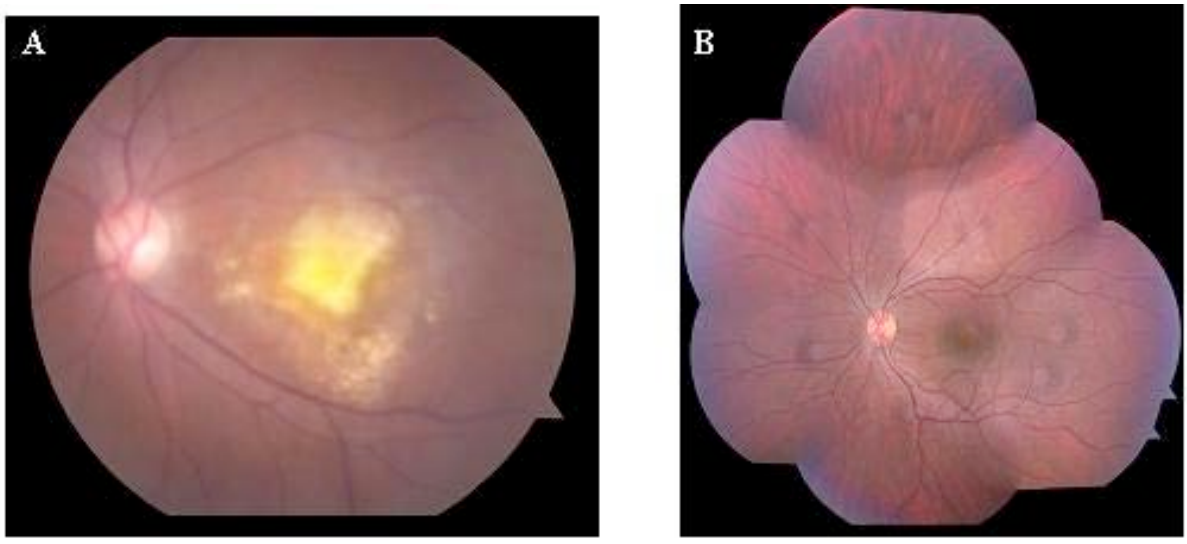

Figure 4. Fundus photos comparing a patient with exudative AMD (**A**) with that of a normal patient (**B**).

The Abca4$^{-/-}$ and the Elovl4 transgenic mice described earlier are useful models of Stargardt Disease and Stargardt-like macular dystrophy respectively. However, the pathologic findings in these mice as well as the association of these genes to AMD make them useful for the investigation of AMD, particularly nonexudative AMD. Because partial loss of Abca4 in knockout mice causes A2E accumulation similar to Stargardt disease and AMD, it has been suggested that the Stargardt disease carrier state may be a predisposing factor to the development of AMD (Mata et al, 2001). The aforementioned Timp3 transgenic mouse used for SFD is also considered as a model for AMD by some due to the overlap of clinical features between SFD and AMD (Rakoczy et al, 2006).

Hypercholesterolemia and diet are two risk factors that have been implicated in the pathogenesis of AMD (van Leeuwen et al, 2003). Consequently, several models of AMD have been developed which involve impaired cholesterol and/or lipid metabolism. One such model that utilized the concept of impaired lipoprotein metabolism was a very low density lipoprotein (VLDL) receptor gene knockout mouse (Heckenlively et al, 2003). A homozygous mutation in the VLDL receptor gene (Vldlr^{tm1Her}) causes retinal angiomatous proliferation, a form of occult CNV. Later, Rudolf and colleagues developed a similar model that utilized a knockout of the low density lipoprotein (LDL) receptor (Rudolf et al, 2005). An accumulation of lipid particles is seen in Bruch's membrane which tends to increase with fat intake. In addition, histology showed vascular endothelial growth factor (VEGF) expression in the outer retinal layers of affected mice and was directly correlated with the amount of lipid particle deposition in Bruch's membrane. No evidence of neovascularization was seen in these mice.

The APOE gene, which encodes apolipoprotein E, has been identified as a risk factor for AMD (Baird et al, 2004). Transgenic mice expressing the APO*E3-Leiden gene (which produces a dysfunctional form of APO-E3) were found to have basal laminar deposits that tended to be more severe in mice consuming a diet high in fat and cholesterol (Kliffen et al, 2000). Dithmar and colleagues were the first to examine the ultrastructural changes in an ApoE (-) model in mice (Dithmar et al, 2000). ApoE deficient mice developed electron-lucent deposits in Bruch's membrane, similar to the basal laminar deposits seen in humans with AMD. A later study by Malek et al combined the risk factors of advanced age and a high fat, cholesterol-rich diet in mice with an ApoE genotype (Malek et al, 2005). Of the different apoE subtypes examined in this study, those deficient in apoE4 were most severely affected and developed many of the pathologic characteristics of AMD. These changes include thickening of Bruch's membrane, atrophy of and pigmentary changes in the RPE, drusenoid deposits, and CNV in some cases. The transgenic C57BL/6 mouse is another combined model that develops hyperlipidemia from the overexpression of human Apo B100 using an Apo B100 gene promoter (Espinosa-Heidmann et al, 2004). Transgenic mice that were treated with blue-green light or were given a high fat diet acquired basal laminar deposits, while transgenic mice that were fed normal diets had no deposits or abnormal morphology. Thus, most models that utilize the impairment of cholesterol or lipid metabolism result in the formation of basal laminar deposits or drusen.

Based on the finding that AMD patients tend to have elevated iron levels in the retina, Hahn et al developed a mouse that was deficient in both ceruloplasmin (Cp) and hephaestin (Heph) (Hahn et al, 2003, 2004). They found that mice that are Cp$^{-/-}$Heph$^{-/Y}$ had increased retinal iron levels. Soon thereafter, affected mice developed RPE death, photoreceptor degeneration, and subretinal neovascularization. As a result, Cp and Heph deficiency leads to increases in ferritin, retinal iron accumulation, and retinal degenerative changes similar to many of the features of AMD. However, the lack of clinically observable drusen is one shortcoming of this model.

Though an increase in amyloid β (Aβ) is typically associated with neurodegenerative diseases, such as Alzheimer's disease, Yoshida and colleagues examined the role of Aβ in the pathogenesis of AMD by disrupting the neprilysin (Mme or Nep) gene in a mouse model (Yoshida et al, 2005). Increased Aβ led to decreased pigment epithelium-derived growth factor (PEDF), RPE degeneration, and basal laminar deposits. Though VEGF was upregulated, there was no observable CNV.

Another genetic modification that has been used to create models of AMD is the impairment of macrophage mobilization. Ambati et al reported the ocular findings in knockout mice that were deficient in monocyte chemoattractant protein-1 (Ccl2) as well as another line of mice deficient in C-C chemokine receptor-2 (Ccr2) (Ambati et al, 2003). Both strains of mice showed similar phenotypic features including thickening of Bruch's membrane, subretinal deposits, drusen, and lipofuscin accumulation. Immune complexes accumulated in the retinas of affected mice, much like humans with AMD, and it was hypothesized that abnormalities in macrophage trafficking contributed to drusen formation. Ccl2$^{-/-}$ and Ccr2$^{-/-}$ mice also exhibited photoreceptor atrophy, outer nuclear layer cell loss, and increased amounts of A2E.

Another mouse model developed by Rakoczy and colleagues is a transgenic heterozygous mouse (mcd/mcd) that expresses an inactive mutant cathepsin D (CatD). It is believed that CatD is involved in photoreceptor outer segment digestion, which is thought to be impaired in patients with AMD (Rakoczy et al, 1999, 2002; Zimmerman et al, 1983). As a result, mcd/mcd mice showed age-related RPE proliferation and atrophy, photoreceptor degeneration, shortened outer segments, lipofuscin, and basal laminar deposits. ERG a- and b-wave amplitudes were also significantly reduced compared to wildtype mice. This model provides supportive evidence that AMD is largely due to the accumulation of abnormal photoreceptor breakdown products in RPE cells.

Certain models of AMD primarily involve the development of choroidal neovascularization for the study of wet AMD. One such model is a transgenic mouse that expresses murine VEGF cDNA coupled to an Rpe65 promoter (Schwesinger et al, 2001). Choroidal neovascularization and blood vessel leakage occurs as a result of increased VEGF expression in this model.

However, choroidal vessels did not penetrate Bruch's membrane into the subretinal space. The most recent model of CNV is a transgenic mouse that expresses prokineticin 1 (hPK1) in the retina using a rhodopsin promoter (Tanaka et al, 2005). Since hPK1 is a mitogen of fenestrated endothelium, it causes enlargement of the fenestrated choroidal vascular bed without affecting the nonfenestrated retinal vasculature. Despite the absence of morphologic changes, histologic analysis showed accumulation of the lipofuscin fluorophore, A2E, in affected mice.

The latest model of AMD reported in the literature involves the impairment of free radical dismutation through a knockout of Cu, Zn-superoxide dismutase (SOD1) in mice (Imamura et al, 2006). Homozygous mice for a deficiency in SOD1 develop thickening of Bruch's membrane, drusen, and CNV, all of which worsen over time. Oxidative damage and degeneration of the RPE was seen on histology, while photoreceptor cell loss occurred in a subset of affected mice. One unique advantage of this model is that the pathologic features seen in these animals tend to be progressive with age, much like AMD in human patients. Our laboratory has also developed a new mouse model of AMD using an RPE65 promoter to overexpress a hypoxia inducible factor-1α (HIF-1α) transgene, which led to the development of drusen-like deposits in the subretinal space (Lin et al, 2006). Autofluorescence images of these animals compared to age-matched controls are shown in **Figure 5A** and **B**.

To date, only one model of AMD has been reported in the rat. Wang and colleagues developed a potential model of exudative AMD by injecting an adeno-associated virus (AAV) encoding human VEGF into the subretinal space of rats (Wang et al, 2003). These rats subsequently developed extensive subretinal neovascularization, photoreceptor degeneration, and blood vessel leakage on fluorescein angiography. ERG amplitudes were also significantly decreased in AAV-VEGF injected eyes.

2. Non-rodent models of age-related macular degeneration

One of the primary challenges of studying macular diseases is the anatomic variation that exists between human eyes and animals. Specifically, the absence of a macula in non-primate species makes them less than ideal for studying a relatively geographically-specific disease process like AMD. However, the difficulty in handling non-human primates as well as their higher cost are some of the major disadvantages that prevent many investigators from using primates as AMD models.

The only evidence of a truly naturally-occurring nonrodent model of AMD was reported in a seminatural colony of aged adult rhesus monkeys at the Caribbean Primate Research Center (CPRC) that were found to have abnormalities consistent with human aging and AMD (Ulshafer et al, 1987). Drusen-like deposits were seen in the inner and outer collagenous zones of Bruch's membrane, and dense bodies were found in both Bruch's membrane and the RPE cytoplasm. A follow-up study in the same colony showed that none of the animals in this sample showed signs of exudative (wet) AMD or disciform scarring, making these animals suitable only for the study of dry AMD (Engel et al, 1988). Since AMD is not a disease of simple Mendelian genetics, no gene was identified in either study that could account for this phenotype. It should be noted that the relatively long lifespan of monkeys requires that they be tracked over a lengthy period of time before they develop signs of macular disease. While this monkey colony presents a unique opportunity to study AMD in a naturally occurring disease model, the drawbacks of using primates for research, as mentioned above, limit the practicality of their use for these purposes. **Table 1** summarizes the characteristics of each model of AMD and the above mentioned macular dystrophies.

III. Retinitis pigmentosa

Retinitis pigmentosa (RP) is a name given to a broad group of inherited diseases that are characterized by progressive rod-cone photoreceptor degeneration, mainly in the peripheral retina, and often result in legal blindness (**Figure 6**). RP affects 1 in 3000 people, which makes it the most common cause of inherited blindness worldwide (Humphries et al, 1992; McKusick, 1998). RP exhibits

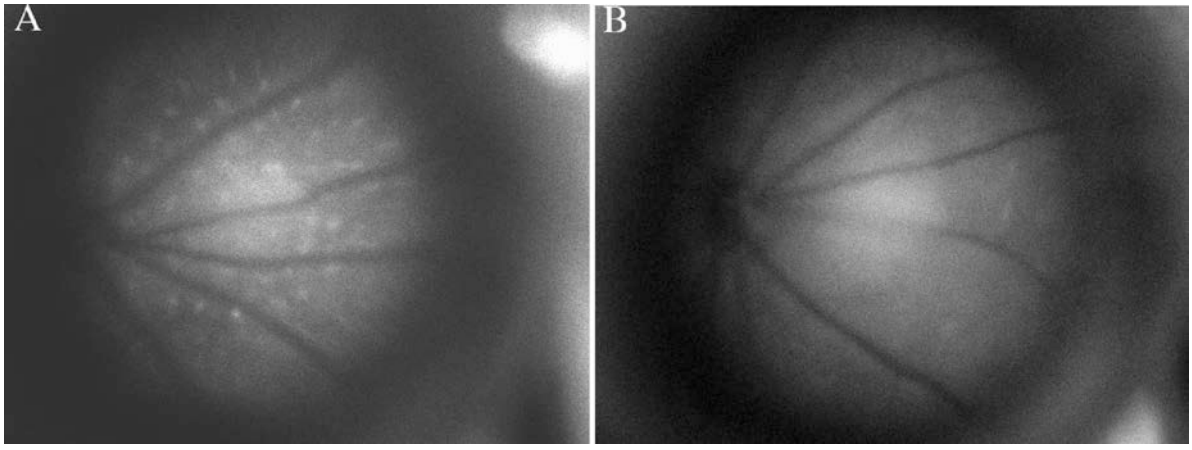

Figure 5. High power autofluorescence image of a HIF1-α transgenic mouse (**A**) with an age-matched control mouse (**B**). Subretinal, drusen-like deposits are clearly seen in the HIF1-α mouse.

Table 1. Genetic models for macular diseases.

Name	Gene	Protein	Modification	Species	Findings	Disease Equivalent
Metabolic proteins						
APO B100	APO B100	APO B100	Transgenic	Mouse	Basal laminar deposits (only when combined with high fat diet or blue-green light exposure)	AMD
ApoE$^{-/-}$	ApoE	ApoE	Knockout	Mouse	Basal laminar deposits; BM thickening, CNV, drusen, and RPE atrophy also seen when combined with old age and high fat/cholesterol diet	AMD
APO*E3-Leiden	APO*E3-Leiden	Apo-E3	Transgenic	Mouse	Basal laminar deposits that increase with fat and cholesterol intake	AMD
LDL-r$^{-/-}$	LDL-r	LDL receptor	Knockout	Mouse	Lipid deposition in BM and VEGF expression in outer retina that increase with fat intake	AMD
Vldlr^{tm1Her}	Vldlr	VLDL receptor	Knockout	Mouse	Retinal and subretinal neovascularization	AMD
Degradation proteins						
NEP$^{-/-}$	*NEP*	Neprilysin	Knockout	Mouse	Basal laminar deposits, RPE degeneration, increased VEGF	AMD
mcd / mcd	CatDM1	Cathepsin D	Transgenic	Mouse	PR degeneration, RPE atrophy and proliferation, lipfuscin, basal laminar deposits, decreased ERG a- and b-waves	AMD
SOD1$^{-/-}$	*SOD1*	Cu, Zn-superoxide dismutase	Knockout	Mouse	Thick BM, CNV, drusen, RPE degeneration, PR atrophy	AMD
Immune function						
Ccl2$^{-/-}$	*Ccl2*	Monocyte chemoattractant protein-1	Knockout	Mouse	Thick BM, drusen, lipofuscin, A2E, PR atrophy, subretinal deposits	AMD

Ccr2$^{-/-}$	*Ccr2*	C-C chemokine receptor-2	Knockout	Mouse	Same as Ccl2$^{-/-}$	AMD
Structural proteins						
Timp3$^{S156C/S156C}$	*Timp3*	Timp3	Knock-in	Mouse	Shortened RPE processes, abnormal PR morphology, thin ONL, thick BM	Sorsby fundus dystrophy, AMD
Transcription factors						
AAV-VEGF	None	VEGF	Transgenic	Rat	CNV, blood vessel leakage, PR degeneration, decreased ERG amplitudes	Wet AMD
HIF1-α	*RPE65* promoter	HIF1-α	Transgenic	Mouse	Hard and soft drusen, irregular choroidal vasculature	Dry AMD
hPK1	*RHO* promoter	hPK1	Transgenic	Mouse	A2E, enlargement of choroidal vessels	Wet AMD
VEGF/RPE65	*RPE65* promoter	VEGF	Transgenic	Mouse	CNV, blood vessel leakage	Wet AMD
Transport proteins						
Cp$^{-/-}$ *Heph*$^{-/Y}$	*Cp, Heph*	Ceruloplasmin, Hephaestin	Transgenic	Mouse	RPE death, PR degeneration, subretinal neovascularization	AMD
Visual cascade						
ABCR $^{-/-}$	*ABCR*	Rim	Knockout	Mouse	Lipofuscin and A2E accumulation, PR degeneration, delayed dark adaptation	Stargardt disease, AMD
ELOVL4	*ELOVL4*	ELOVL4	Transgenic	Mouse	Lipofuscin and phagosome accumulation in RPE, localized PR degeneration, decreased ERG b-wave	Stargardt-like macular dystrophy, AMD
Wt-bestrophin	*VMD2*	Bestrophin	Transgenic	Rat	ERG changes	Best Disease
Others						
CPRC Monkey	Unknown	Unknown	None	Primate	Drusen, BM abnormalities	Dry AMD

Abbreviations: A2E, N-retinylidene-N_retinylethanolamine; AMD, age-related macular degeneration; BM, Bruch's membrane; CNV, choroidal neovascularization; ERG, electroretinogram; ONL, outer nuclear layer; PR, photoreceptor; RPE, retinal pigment epithelium

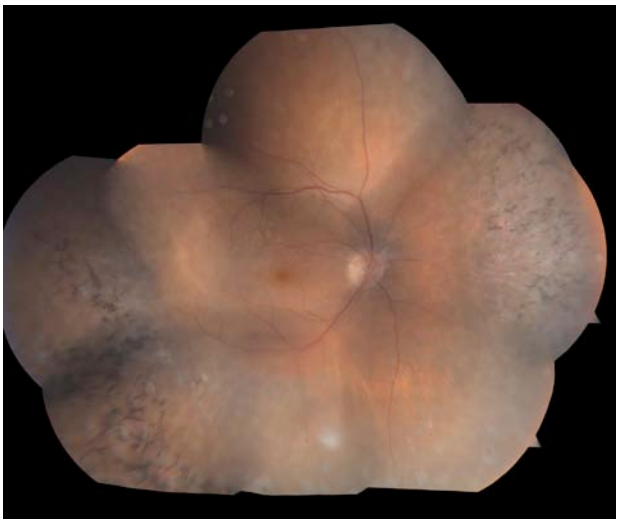

Figure 6. Fundus photo taken from a patient with retinitis pigmentosa. The appearance of intra-retinal pigmentation is most prominent in the mid-periphery early in the course of the disease. RPE migration and retinal atrophy is illustrated.

multiple patterns of inheritance, including autosomal dominant, autosomal recessive, sex-linked, and mitochondrial inheritance patterns (Dryja and Berson, 1995). A study conducted in Maine showed the frequency of these inheritance patterns as follows: 19% dominant, 19% recessive, 8% X-linked, 46% isolates and 8% undetermined (Dryja and Li, 1995). The majority of the isolated cases of RP probably involve recessive inheritance. Initially, RP presents with night blindness due to the progressive loss of rod photoreceptor cells. Subsequently, affected individuals develop tunnel vision and eventually, complete loss of sight as the cones also degenerate. ERGs tend to be abnormal in affected individuals before the onset of symptoms (Berson et al, 1969; Humphries et al, 1992).

Despite the high prevalence of RP among inherited photoreceptor degenerative diseases, it was not until the past decade (1990) that it was discovered that mutations in the rhodopsin gene could cause autosomal dominant RP (Dryja et al, 1990; Pacione et al, 2003). It is now known that photoreceptor specific gene defects account for many forms of RP (Dryja and Berson, 1995; Humphries et al, 1992; Lindsay et al, 1992; Rosenfeld and Dryja, 1995). Some involve alterations in rhodopsin, while some cause changes in structural proteins such as peripherin/RDS or ROM-1 (Humphries et al, 1992; Rosenfeld and Dryja, 1995). Others involve defects in the signal transduction mechanism, such as the α and β subunits of cyclic guanosine monophosphate phosphodiesterase (cGMP PDE) (Huang et al, 1995; McLaughlin et al, 1995). Why such gene defects cause rods to degenerate is unknown. The problem is intriguing, because some rhodopsin and PDE gene defects eliminate rod function but do not lead to any further degeneration, resulting in stationary night blindness (Dryja et al, 1990; Gal et al, 1994). More often, however, rod specific gene defects cause a degeneration of rods first, and then a degeneration of cones later.

A. Autosomal-dominant retinitis pigmentosa

A number of photoreceptor-specific gene defects have been implicated in the etiology of the autosomal dominant form of RP (Dejneka et al, 2003). Mutations involved in dominant disease tend to cause a mutant protein with an unwanted gain of function. It is estimated that roughly 15-35% of all cases of RP are due to autosomal-dominant inheritance (Ayuso et al, 1995; Bunker et al, 1984; Novak-Laus et al, 2002).

1. Rodent models of autosomal-dominant retinitis pigmentosa

In 1975, the Wag/Rij rat was reported as a new spontaneously occurring model of an early onset retinal degeneration similar to RP (Lai et al, 1975). This model was initially thought to be valuable, because it displayed the slowest progression of photoreceptor cell death compared to other models (Lai et al, 1975; Lai and Jonas, 1977). About a decade later, subsequent studies failed to reproduce the findings reported originally by Lai and colleagues (LaVail et al, 1987). As a result, the Wag/Rij rat has proven to be suitable as a model of epilepsy but is not currently considered useful in the study of RP (Aker et al, 2006; Citraro et al, 2006).

The retinal degeneration slow (rds) mouse has a loss of function mutation in the gene Prph2 that encodes a photoreceptor-specific membrane glycoprotein called peripherin (Dalke and Graw, 2005; Dejneka et al, 2003; Van Nie et al, 1978). The rds mouse is also known as rd2 (retinal degeneration 2) or $Prph2^{Rd2}$, the name of the affected gene. Some of the most striking phenotypic features in homozygous rds mice are the absence of photoreceptor outer segments and a receptor layer that consists only of inner segments (Sanyal and Jansen, 1981). Compared to the retinal degeneration (rd) mouse discussed below, the rds mouse undergoes slow and specific photoreceptor death leading to thinning of the outer nuclear layer (Sanyal, 1987).

A mutation in the gene RP1 (retinitis pigmentosa 1) has been associated with autosomal dominant RP in several linkage studies (Blanton et al, 1991; Berson et al, 2001; Bowne et al, 1999; Guillonneau et al, 1999; Jacobson et al, 2000; Pierce et al, 1999; Sullivan et al, 1999). RP1 encodes a protein of unknown function whose N-terminus resembles human doublecortin (DCX), which interacts with microtubules (des Portes et al, 1998;

Gleeson et al, 1999; Horesh et al, 1999). Therefore, Gao et al developed a model of progressive photoreceptor degeneration using targeted disruption of Rp1h (formerly known as Rp1) in mice (Gao et al, 2002). Mice with a homozygous knockout of Rp1h experience progressive rod-cone degeneration over a period of one year due to mislocalization of rhodopsin. The number of cone photoreceptors did not change until about 10 months of age. Morphologically, both rods and cones were found to be abnormal in structure and became progressively shorter over time. ERG amplitudes were also significantly decreased when compared to heterozygous mice or mice without the Rp1h mutation.

Rod photoreceptor cells use a photoreactive pigment called rhodopsin (Rho), and genetic linkage has been clearly established between RP and abnormalities in the RHO gene (McWilliam et al, 1989). Consequently, most genetic models of RP involve some sort of mutation in the gene for Rho. In 1992, Olsson et al developed a transgenic mouse model of autosomal dominant RP with a substitution of histidine for proline (P23H) at codon 23 of the rhodopsin gene (Olsson et al, 1992). This substitution in the rhodopsin gene is found in approximately 12% of patients with autosomal dominant RP. This mutation leads to overexpression of rod opsin, which leads to a retinal degeneration that is similar to that seen in human RP. Rho accumulates in the outer nuclear layer of the retina, suggesting that mutant Rho may utilize a different intracellular pathway than that used by normal rhodopsin (Roof et al, 1994).

Later, Lewin and colleagues rescued the P23H mutation in a transgenic rat using AAV vectors to develop a model with a phenotype similar to humans with RP (Lewin et al, 1998). This substitution causes a mutation in opsin transgene expression beginning on postnatal day 5. Abnormalities become apparent beginning on day 15, with an increase in pyknotic photoreceptor nuclei in the outer nuclear layer of the retina. Affected rats undergo slow rod degeneration with normal cone function initially (Machida et al, 2000). Over time, rod outer segments shorten and outer nuclear layer cells are lost. A-wave amplitudes are also significantly smaller compared to controls on scotopic ERGs.

The VPP mouse is a variant of the P23H mouse that involves three mutations (Goto et al, 1995; Naash et al, 1993). In addition to P23H, the VPP mouse also carries the following mutations near the N-terminus of opsin (a rhodopsin apoprotein): glycine for valine at position 20 (V20G) and leucine for proline at position 27 (P27L). It should be noted that V20G and P27L, which improved antibody epitope recognition, are not associated with human RP. Affected mice undergo shortening of rod outer segments and loss of photoreceptor nuclei (Naash et al, 1993). In addition, there is a decrease in photoreceptor Rho content (Goto et al, 1995; Naash et al, 1993, 1996). Rod-mediated ERGs in VPP mice show decreased amplitudes at 1 month that continue to decline over time (Goto et al, 1995). Cone-mediated ERGs remain intact until 5 months of age, at which time a progressive decline is also seen. A model utilizing a complete knockout of the Rho gene was later reported in 1997 (Humphries et al, 1997). Homozygous mice ($Rho^{-/-}$) do not elaborate rod outer segments and undergo uniform loss of photoreceptors that is complete by 3 months. In addition, the rod ERG is extinguished. Heterozygous mice show some structural disorganization of the inner and outer segments but retain the majority of their photoreceptors (Calvert et al, 1999; Humphries et al, 1997).

The mutation Q344ter causes the absence of the last 5 amino acids in the C terminus of Rho and has been linked to functional abnormalities in autosomal dominant RP (Jacobson et al, 1994; Sung et al, 1994; Vaughan et al, 2003). Mice that express this transgene exhibit impaired Rho transport to the rod outer segment (Sung et al, 1994). Q344ter mice undergo progressive photoreceptor degeneration and thinning of the outer nuclear layer. In addition, transgenic rods displayed a later implicit time on ERGs.

A similar transgenic model in rats that involves abnormalities in Rho is the S334ter mutation. In these animals, a termination codon at residue 334 leads to the production of a truncated opsin protein (Steinberg et al, 1996). Unlike Q344ter, the S334ter mutation is only a feature of animal models and is not seen in human autosomal dominant RP. Affected rats undergo rapid retinal degeneration, losing over half of their photoreceptors by postnatal day 2 (Liu et al, 1999). It has been proposed that caspase-3 activation may play a part in the rapid rate of photoreceptor death seen in these rats. In addition, rats with the S334ter mutation undergo thinning of the outer nuclear layer and diminished ERGs relative to wildtype rats (Martin et al, 2004)

2. Nonrodent models of autosomal-dominant retinitis pigmentosa

Hereditary rod-cone degeneration was first noted in the Abyssinian cat in 1985 (Narfstrom et al, 1985). Further studies to characterize the retinal degeneration in these animals showed that a slowly progressive, generalized retinal atrophy occurs at approximately 2 years of age with photoreceptor degeneration of rods first, and then both rods and cones later (Narfstrom and Nilsson, 1987). Since then, this strain of cats has been referred to as the retinal dystrophy (rdy) cat and has garnered interest as a legitimate model of autosomal dominant retinitis pigmentosa (Gould and Sargan, 2002). A study to identify the gene responsible for the rdy phenotype excluded PDE6G (PDE-6-γ) and ROM1 (retinal outer membrane 1) as candidate genes, and genetic sequencing of RHO showed that rhodopsin was unlikely to be a candidate gene as well (Gould and Sargan, 2002).

Another model of autosomal-dominant RP that has the distinct advantage of having many anatomical similarities to the human retina is the Pro347Leu (P347L) rhodopsin transgenic pig (Petters et al, 1997). Compared to rodents, pigs have a much more human-like globe size and cone:rod ratio in the retina. However, the drawbacks of using such a model include the high cost of these animals as well as the difficulty in handling them. The rhodopsin P347L transgenic pig develops severe, early rod degeneration with complete rod death by 20 months (Li et al, 1998). Progressive degeneration of cones is also seen,

but at a much slower rate than rods. Histology shows that these pigs display short outer segments and stacks of Rho-positive membranes in the inner segments. Misrouting of mutant Rho appears to contribute to early rod cell death.

A point mutation (Thr4Arg) in the RHO gene has been shown to be responsible for a naturally occurring model of autosomal dominant RP in the English Mastiff dog (Kijas et al, 2002). As a result, this is the only mammal with a naturally occurring mutation in the RHO gene causing visual impairment. There is topographic variation of photoreceptor degeneration in the early stages, with the most severe disease in the area of the optic nerve head. While rods degenerate before cones, end stage atrophy results in progressive loss of all photoreceptors and the RPE. Like humans with RP, RHO mutant dogs displayed abnormal photoreceptor adaptation on ERG.

B. Autosomal-recessive retinitis pigmentosa

RP most commonly occurs in an autosomal recessive fashion (Hartong et al, 2006). This form of RP tends to occur as a result of lack-of-function mutations in genes that are involved in the visual transduction cascade as well as photoreceptor outer segment maintenance (Dejneka et al, 2003). Numerous genes have been identified in the etiology of RP. For example, the RPE based gene, MERTK (MER tyrosine kinase), is involved in the RPE phagocytic pathway, and loss of function in this gene can cause retinal degeneration as a result (D'Cruz et al, 2000). The investigation of recessive RP has a distinct advantage in that there are several useful animal models that develop spontaneous retinal degeneration. These include both rodents as well as higher species, including dogs and cats.

1. Rodent models of autosomal-recessive retinitis pigmentosa

One of the most commonly used mouse models of retinal pathology is called the retinal degeneration (rd1) mouse, whose abnormality has been localized to chromosome 5 (Sidman and Green, 1965). Also known as rd1 and $Pde6b^{rd1}$, retinal degeneration in this model is inherited as an autosomal recessive trait. The rd1 mouse carries a null mutation in the Pde6β gene, which encodes the β subunit of PDE in rod photoreceptors (Lolley, 1994). As a result, affected mice undergo early, progressive degeneration of the outer retina and complete loss of rod photoreceptors by day 36 (Carter-Dawson et al, 1978). Cones degenerate at a much slower rate in comparison, while other retinal cells remain fairly intact (Carter-Dawson et al, 1978).

A more recent model utilizing a defect in retinal cGMP PDE was developed by Tsang and colleagues (Tsang et al, 1996). A homozygous mutant allele in the gamma subunit of PDE causes a rapid and severe retinal degeneration that resembles autosomal recessive RP in humans. ERGs of homozygous mutants show severely diminished a- and b-wave amplitudes as well as a delayed b-wave implicit time. Outer segments become shortened and disorganized, and by 8 weeks of age, the photoreceptor layer is completely lost. A later study by the same group examined whether the antiapoptotic Bcl2 gene could rescue the retinal degeneration seen in homozygous $Pdeg^{tm1}/Pdeg^{tm1}$ mice (Tsang et al, 1997). Using ERGs and histology, it was shown that mice carrying the Bcl2 transgene experienced partial and temporal delay of the photoreceptor degeneration typically found in mutant mice.

Mutations in the tubby gene family are also a known cause of retinal degeneration (Hagstrom et al, 1999). The gene, tubby-like protein 1 (TULP1), is a member of the tubby family that has been linked to autosomal recessive RP in several linkage studies (Banerjee et al, 1999; Gu et al, 1999; Hagstrom et al, 1998). TULP1 encodes a photoreceptor protein of unknown function that is necessary for rod and cone viability (Hagstrom et al, 1999). In mammals, genetic mutations of tubby or TULP is associated with three distinct disease phenotypes: obesity, retinal degeneration, and hearing loss (Boggon et al, 1999). As a result, a homozygous knockout of Tulp1 ($Tulp1^{-/-}$) causes early onset, progressive retinal degeneration affecting both rods and cones. Scotopic and photopic ERGs in homozygous mice are diminished, and massive vesicle accumulation is seen in the interphotoreceptor matrix. Shortened, disorganized outer and inner segments are seen on microscopy.

One of the most commonly used spontaneous rodent models of autosomal recessive RP is the Royal College of Surgeons (RCS) rat (LaVail, 2001; Strauss et al, 1998). Retinal degeneration in this model is due to a mutation in the MERTK gene, which encodes a receptor tyrosine kinase (MER protein) that is responsible for proper phagocytosis of shed rod outer segments by the RPE (D'Cruz et al, 2000). Photoreceptors degenerate slowly in the RCS rat until complete loss occurs at approximately 6 months of age (Dowling and Sidman, 1962; LaVail and Battelle, 1975). Despite photoreceptor degeneration, morphologic studies show that the inner retinal architecture remains fairly normal (Ball et al, 2003a). In 2003, retinal degeneration in the Mertk knockout mouse, which was originally developed by Camenisch and colleagues, was reported (Camenisch et al, 1999; Duncan et al, 2003). Similar to the RCS rat, the Mertk knockout mouse exhibited progressive photoreceptor degeneration, absence of phagosomes in the RPE at the peak of outer segment disc shedding, accumulation of debris in the outer segment-RPE interface, and slow removal of pyknotic photoreceptor nuclei (Duncan et al, 2003). Their study showed that ablation of MER function resulted in decreased scotopic ERG readings and a similar retinal phenotype as the RCS rat on histology.

Mutations in the ABCA4 gene for Stargardt disease have also been linked to some cases of cone-rod dystrophies as well (Cremers et al, 1998). However, the clinical features seen in Abca4 knockout mice more closely mimic human Stargardt maculopathy, and as a result, this mouse is not commonly used as a model for the biochemical features of RP.

2. Nonrodent models of autosomal-recessive retinitis pigmentosa

Much has been learned about recessive RP from the use of companion animals as disease models. One of the

most well-established disease models is the rod-cone dysplasia (rcd1) seen in Irish setter dogs (Aguirre et al, 1978; Aguirre et al, 1982; Liu et al, 1979; Suber et al, 1993). The rcd1 phenotype is caused by a nonsense mutation that produces a nonfunctional rod cGMP PDE β subunit (Suber et al, 1993). Histologic examination shows that affected animals have a fragmented outer segment, diminutive inner segments, and progressive photoreceptor and outer nuclear layer degeneration (Pearce-Kelling et al, 2001). Both rod and cone b-waves are either absent or decreased on ERG when compared to control animals.

Around the same time that the rcd1 setter dog was first discovered, a recessively inherited retinopathy was reported in the collie dog (Wolf et al, 1978). The rod-cone dysplasia seen in the collie is now known as rcd2 (Santos-Anderson et al, 1980; Woodford et al, 1982; Wolf et al, 1978). Rod and cone outer segments fail to develop normally and undergo subsequent degeneration. Cones degenerate slower than rods, and histologic changes are similar to those seen in the rcd1 Irish setter dog. Affected collie dogs have more severe changes electrophysiologically and ophthalmoscopically at an earlier age than the Irish setter (Santos-Anderson et al, 1980). However, the gene responsible for the phenotype of the rcd2 collie has not been identified.

In addition, an extended pedigree of Cardigan Welsh corgi dogs has been studied as a potential model of autosomal recessive RP (Petersen-Jones et al, 1999). A single base deletion in the Pde6A gene, which encodes the α subunit of cGMP PDE, was found to be responsible for retinopathy in affected dogs. Degenerative changes can be seen on ophthalmoscopy at 6-16 weeks of age, but progressive retinal atrophy occurs slowly over time, with some animals retaining limited central vision for up to 3-4 years (Keep, 1972). As a result, this line of dogs is categorized as rod-cone dysplasia 3 (rcd3) (Petersen-Jones et al, 1999).

An early onset, autosomal recessive, progressive retinal dystrophy in a colony of Persian cats was reported recently by Rah and colleagues (Rah et al, 2005). Clinical and histologic evidence from their study shows that retinal degeneration occurs early in life (approximately 3 weeks of age) and progresses rapidly until there is complete loss of photoreceptor cells by 17 weeks. Scotopic and photopic ERGs were nonrecordable in affected animals, suggesting that both rods and cones undergo degeneration. Although the causal gene was not identified in the study, the authors point out that many of the histologic features of these Persian cats mimic those seen in other models of rod-cone degeneration, such as the rcd2 collie (Santos-Anderson et al, 1980; Rah et al, 2005).

C. X-linked retinitis pigmentosa

In contrast to other forms of RP, X-linked RP, also known as RP3, has an early age of onset as well as early involvement of both rods and cones (Bauer et al, 1998; Berson et al, 1980; Buraczynska et al, 1997; Fishman et al, 1998; Jacobson et al, 1997; Weleber et al, 1997). Affected teenage males experience severe degeneration of rods followed closely by degeneration of cones and retinal atrophy (Zeiss et al, 2000). Female carriers undergo a patchy distribution of rod degeneration that is consistent with X chromosome inactivation (Zeiss et al, 2000). The retinitis pigmentosa GTPase regulator (RPGR) gene has been implicated as a major cause of X-linked RP (Meindl et al, 1996). The exact function of the RPGR protein remains unclear, however. It has been proposed that RPGR is involved in the maintenance of outer segment specific proteins, which makes it essential for photoreceptor viability (Hong et al, 2000).

1. Rodent models of X-linked retinitis pigmentosa

After the identification of RPGR as a causal gene in X-linked RP, a Rpgr knockout mouse model was subsequently developed (Hong et al, 2000). Histologic analysis showed that mutant mice exhibited ectopic localization of cone opsins in the cell body and synapses, while decreased levels of rhodopsin were seen in rod photoreceptors (Hong et al, 2000). Eventually, both cones and rods degenerate. In their study, RPGR was localized to the connecting cilia of rod and cone photoreceptors (Hong et al, 2000). As a result, they hypothesize that RPGR is involved in maintaining the polarized protein distribution across the connecting cilium by facilitating directional transport or restricting redistribution.

2. Nonrodent models of X-linked retinitis pigmentosa

To date, the Siberian husky dog is the only known naturally occurring model of X-linked RP in a companion animal (Acland et al, 1994). Electron microscopy of the XLPRA (X-linked progressive retinal atrophy) dog shows vesiculation of rod discs and disruption of outer segments. Eventually, there is a loss of cones and progressive atrophy of the inner retinal layers as well (Zeiss et al, 1999). The most significant lesions are seen in the peripheral retina with advancement to the area of the optic nerve (Zeiss et al, 1999). ERGs of affected male dogs and homozygous females showed decreased b-wave amplitudes consistent with these histopathologic abnormalities. The canine XLPRA phenotype has been linked to the gene RPGR, and homology of canine XLPRA and human RP3, an X-linked form of RP, has been established (Zeiss et al, 2000; Zhang et al, 2001a).

In addition to companion animals, a blind mutation known as retinal dysplasia and degeneration (rdd) has been reported in chickens since 1980 (Kondoh et al, 1980; Randall et al, 1983; Wilson et al, 1982). Affected animals have a significant reduction in photoreceptors and progressive retinal thinning secondary to cell loss in the photoreceptor and inner nuclear layers (Burt et al, 2003). While it is still unclear which gene(s) is responsible for the clinical phenotype in the rdd chicken, a linkage study by Burt and colleagues have proposed that PDE6A, which encodes the α subunit of cGMP PDE, is a possible candidate (Burt et al, 2003). It is still yet to be determined whether the rdd chicken is a direct human equivalent of RP or whether it represents a different disease process. **Table 2** summarizes the features of genetic RP models by functional class of the affected gene.

Table 2. Genetic models of retinitis pigmentosa

Name	Gene	Protein	Modification	Species	Findings	Disease Equivalent
Degradation proteins						
mer^{kd}	*MER*	MER protein	Knockout	Mouse	Rapid, progressive PR degeneration, debris in RPE-outer segment interface, decreased scotopic ERG	ARRP
RCS	*MERTK*	MER protein	Naturally-occurring	Rat	Slow, progressive PR degeneration	ARRP
Structural proteins						
rcd2	Unknown	Unknown	Naturally-occurring	Collie dog	Rod-cone degeneration, decreased ERGs	ARRP
rds (rd2, Prph2)	*Prph2*	Peripherin	Naturally-occurring	Mouse	Absent PR outer segments, PR degeneration, ONL thinning	ADRP
RP1$^{-/-}$	*RP1*	RP1 protein	Knockout	Mouse	Progressive rod-cone degeneration, decreased ERGs	ADRP
RPGR$^{-/-}$	*RPGR*	RPGR protein	Knockout	Mouse	PR degeneration, decreased RHO, decreased ERG	XLRP
Visual cascade						
P23H	*RHO*	RHO	Transgenic	Mouse, rat	Progressive rod-cone degeneration, PR death, ONL cell loss, decreased scotopic ERGs	ADRP
P347L	*RHO*	RHO	Transgenic	Pig	Progressive rod-cone degeneration, shortened outer segments	ADRP
Q344ter	*RHO*	RHO	Transgenic	Mouse	Progressive PR degeneration, ONL thinning, increased ERG implicit time	ADRP
RHO$^{-/-}$	*RHO*	RHO	Knockout	Mouse	PR degeneration, absent rod ERG	ADRP
S344ter	*RHO*	RHO	Transgenic	Rat	Rapid PR degeneration, ONL thinning, decreased ERG	ADRP
Thr4Arg	*RHO*	RHO	Naturally-occurring	English Mastiff dog	Progressive rod-cone degeneration, RPE loss, abnormal ERG	ADRP
VPP (V20G, P23H, P27L)	*RHO*	RHO	Transgenic	Mouse	PR degeneration, decreased RHO, progressively	ADRP

Pdeg^{tm1}/Pdeg^{tm1}	*Pde6g*	Gamma subunit of cGMP-PDE	Knockout	Mouse	PR loss, outer segment shortening and disorganization, decreased ERG a- and b-wave	ARRP
rcd1	*Pde6b*	Beta subunit of cGMP-PDE	Naturally-occurring	Irish Setter dog	Progressive PR and ONL degeneration, decreased ERG b-wave	ARRP
rcd3	*Pde6a*	Alpha subunit of cGMP-PDE	Naturally-occurring	Cardigan Welsh corgi dog	Slowly progressive retinal atrophy	ARRP
rd (rd1)	*Pde6b*	Beta subunit of cGMP-PDE	Naturally-occurring	Mouse	Progressive rod-cone and outer retinal degeneration	ARRP
tulp1$^{-/-}$	*TULP1*	TULP1 protein	Knockout	Mouse	Early onset progressive rod-cone degeneration, extracellular vesicles, diminished ERG	ARRP
Others						
Early onset PRA Persian cat	Unknown	Unknown	Naturally-occurring	Persian cat	Early, rapidly progressive PR degeneration, absent ERG	ARRP
rdd	Unknown	Unknown	Naturally-occurring	Chicken	PR death, retinal thinning	XLRP
rdy	Unknown	Unknown	Naturally-occurring	Abyssinian cat	Progressive rod-cone degeneration, retinal atrophy	ADRP
XLPRA Siberian husky dog	Unknown	Unknown	Naturally-occurring	Siberian husky dog	Progressive rod-cone degeneration, inner retinal atrophy, decreased ERG b-wave	XLRP

Abbreviations: ADRP, autosomal dominant retinitis pigmentosa; ARRP, autosomal recessive retinitis pigmentosa; ERG, electroretinogram; ONL, outer nuclear layer; PR, photoreceptor; RPE, retinal pigment epithelium; XLRP, X-linked recessive retinitis pigmentosa

D. Usher syndrome

RP can also be seen as part of a syndrome characterized by systemic signs and symptoms in addition to the progressive visual impairment typically associated with the disease (Hartong et al, 2006). Two of the most well-documented syndromes involving RP are Usher syndrome (USH) and Bardet-Biedl syndrome (BBS). USH is the most common RP syndrome (Boughman et al, 1983; Heckenlively et al, 1988). Affected patients suffer early-onset hearing loss in combination with RP and areflexia in an autosomal recessive pattern of inheritance. USH is divided into three subtypes, USH1 – USH3, based on the severity of the clinical symptoms and the genes involved (Koenig, 2003). As a result, the pathogenesis of each type differs. Defects in cilial cells are seen in USH1, while abnormalities of basement membranes are the cause of USH2. In contrast, USH3 is thought to be caused by synaptic differences (Koenig, 2003).

1. Models of Usher syndrome

The tubby (tub) mouse, also known as the retinal degeneration 5 (rd5) mouse, has a homozygous (rd5/rd5) defect in the tub gene, which leads to retinal degeneration and neurosensory hearing loss in combination with obesity (Noben-Trauth et al, 1996). Affected mice exhibit reduced ERG amplitudes which are extinguished by 6 months of age (Heckenlively et al, 1995). There is focal and diffuse loss of the RPE, with patches of pigment deposits on

indirect ophthalmoscopy. Photoreceptors and the outer nuclear layer undergo progressive degeneration, and by 8 months of age, no photoreceptors are present. Inner ear histology also shows loss of both inner and outer ear hair cells in the organ of Corti by 6 months. While the molecular genetics of the rd5 mouse are not completely understood, it is thought that the tub mutation is not associated with a primary axonemal defect (Ohlemiller, 1998). However, it is clear that mutations in the tub gene family (e.g. tubby-like proteins) are involved in retinal degeneration (Ikeda et al, 2000).

The inbred mouse strain RBF/DnJ was the first proposed model for type IIA USH in 1997 (Pieke-Dahl et al, 1997). Retinal degeneration in this mouse is caused by a defect in retinal degeneration 3 (rd3), which is a recessive gene that has been localized to mouse chromosome 1 (Chang et al, 1993). This is orthologous to the location of the USH2A gene in humans (DeBry and Seldin, 1996). Retinal degeneration due to rd3 is characteristic of a progressive rod-cone dystrophy beginning at about 2 weeks of age (Chang et al, 1993). Unlike the rd or rds mouse, initial photoreceptor development until that time is thought to be normal. There are no reports of hearing or vestibular abnormalities in mice that are homozygous only for rd3. However, Pieke-Dahl and colleagues found that RBF/DnJ mice develop progressive high frequency hearing loss, which may be independent of the rd3 gene (Pieke-Dahl et al, 1997).

Several mouse models of USH in the literature develop hearing loss but fail to demonstrate the progressive retinal degeneration that is characteristic of this disease. The Ames waltzer (av) mouse is one such animal model of USH1F, due mainly to the severe vestibular and auditory impairment seen in affected animals (Raphael et al, 2001). Hearing loss in affected mice is due to a recessive mutation in the Pcdh15 gene, which encodes a protein called protocadherin (Ahmed et al, 2001; Alagramam et al, 2001). Ahmed and colleagues showed that PCDH15 is expressed in the retina and may contribute to both RP and hearing loss in affected USH1F patients (Ahmed et al, 2001). However, a study of ERG and histology in av mice did not find any retinal abnormalities due to mutations in Pcdh15 (Ball et al, 2003b). A more recent study confirmed the lack of histologic changes on retinal sections, but did find attenuated scotopic ERG amplitudes in affected mice (Haywood-Watson et al, 2006). As a result, mutations in Pcdh15 do not accurately mimic the RP seen in human USH1F.

The waltzer (v) mouse has also been proposed as an animal model of USH1D because of the development of hearing loss secondary to a defect in the Cdh23 gene (Di Palma et al, 2001). Specifically, Cdh23 encodes a type of cadherin that is expressed in the sensory hair cells of the cochlea (Di Palma et al, 2001; Wilson et al, 2001). A later study of the relationship between retinal function and Cdh23 found that mutations in this gene do in fact cause retinal dysfunction, but not retinal degeneration (Libby et al, 2003). Retinal histology shows no signs of photoreceptor degeneration or anatomic abnormalities, although some changes were noted in ERGs of mutant mice.

Myosin VIIa (MYO7A) is a gene that has been linked to USH1B (Weil et al, 1997). It is involved in deafness at the mouse equivalent Myo7a locus and has been proposed as a model of USH1B (Gibson et al, 1995). Previously, this model was called the shaker1 (sh1) mouse. Though myosin VIIa is present in the RPE and photoreceptors, mutations in MYO7A have not been shown to cause retinal degeneration in affected mice with hearing loss (el-Amraoui et al, 1996; Hasson et al, 1995; Liu et al, 1997, 1999). Like the waltzer mouse however, Libby and Steel showed that the sh1 mouse has decreased ERG amplitudes in spite of normal retinal structure (Libby and Steel, 2001).

Hearing impairment has also led to the use of a strain of BUB/BnJ ($Mass1^{frings}$) mouse as a model of USH IIC (Johnson et al, 2005; Klein et al, 2005). The responsible defect is a nonsense mutation found in the monogenic audiogenic seizure-susceptible gene (MASS1) (Skradski et al, 2001). It is thought that MASS1 is involved in the transcription of a very large G-protein couple receptor family (VLGR1) whose function is unknown (McMillian et al, 2002). However, visual defects have not been reported in this model. As a result, it appears that the $Mass1^{frings}$ mouse, like the av, v, and Myo7a mice, is a good model for the hearing loss seen in USH but is challenging for studying the retinal degeneration associated with the human disease.

Recently, a knock-in mouse containing the Ush1c216A mutation was developed to mimic USH1C (Lentz et al, 2006). The introduction of the 216G→A splice site mutation, found in some patients with USH1C, caused circling and head tossing behavior that are characteristic in deaf mice. However, it is not known whether these mice develop progressive retinal degeneration as well.

E. Bardet-Biedl syndrome

BBS is a genetic disorder in which retinopathy is seen as part of a constellation of systemic symptoms including obesity, polydactyly, mental retardation, hypogenitalism, and renal abnormalities of varying severity. In addition, cardiac anomalies, ataxia, poor coordination, and hearing loss have also been reported. To date, twelve BBS loci, named BBS1 – BBS12, have been uncovered (Koenig, 2003; Stoetzel et al, 2007). Of these, BBS1 is the most common, accounting for almost half of all cases of BBS (Mykytyn et al, 2002). However, it is still unclear what the exact function of the BBS proteins are.

1. Models of Bardet-Biedl syndrome

Thus far, animal models of BBS have only been found in rodents. Mice that possess a null mutation in the BBS genes have displayed a phenotype mimicking the multiorgan involvement seen in human BBS. There are currently three knockout mouse models of BBS which involve a lack of expression of one of the BBS proteins - $Bbs2^{-/-}$, $Bbs4^{-/-}$, and $Bbs6^{-/-}$ (also known as MKKS). The first model to be reported was the Bbs4-null mouse, which possesses many of the features seen in human BBS,

including obesity and retinal degeneration (Mykytyn et al, 2004). Lack of proper Bbs4 expression results in failure of flagella synthesis during spermatogenesis. However, ciliogenesis remains intact. While the loss of Bbs4 does not appear to affect the initial formation of photoreceptor outer segments, it has been proposed that intracellular transport required for maintenance of the outer segments is somehow compromised leading to retinal degeneration. In contrast, the Bbs2 knockout mouse has renal cysts and defects in olfaction in addition to retinopathy, obesity, and impaired spermatogenesis (Nishimura et al, 2004). In $Bbs2^{-/-}$ retinopathy, the initial development of the retina is normal, but this is soon followed by apoptotic photoreceptor death secondary to mislocalization of rhodopsin. Both the Bbs4 and Bbs2 knockout mice show deficits in social interaction as well.

BBS6 is a gene that is also known as MKKS, because of its relationship to an autosomal recessive disorder called McKusick-Kaufman syndrome (MKS), which has many clinical features that overlap with BBS. A small percentage of BBS cases are due to a defect in MKKS. As a result, Fath and colleagues developed a knockout mouse of the Mkks gene which resulted in another animal model with a phenotype resembling BBS (Fath et al, 2005). Like the Bbs2 and Bbs4 knockout mice, these animals developed retinopathy, impaired spermatozoa flagella formation, and obesity. In addition, there was elevated blood pressure and deficits in olfaction and social dominance. Retinas appeared normal early in life, but by 8 months, the outer nuclear layer was completely degenerated and the presence of inner and outer segments was not detectable.

One mouse model that does not involve the impairment of BBS gene expression is the tubby mouse described above. Since BBS can be characterized partially as a human obesity syndrome, the phenotypic similarity of this model combined with the presence of retinopathy makes the tubby mouse an adequate model for BBS as well as USH (Noben-Trauth et al, 1996; Ohlemiller et al, 1995). Key features of the genetic models of RP-related syndromes are listed in **Table 3**.

IV. Cone disorders

In contrast to RP and other rod-cone dystrophies, cone disorders are a heterogenous group of diseases that are characterized by deficiencies in color vision, loss of day vision, central scotoma, photophobia, and nystagmus (Michaelides et al, 2003a). They are not as prevalent as rod-cone dystrophies, and they may have either a stationary or progressive course. Stationary cone diseases tend to be congenital and affected patients retain normal rod function. Progressive cone dystrophies (and also cone-rod dystrophies), on the other hand, usually present during childhood or early adolescence with eventual deterioration of rod function as well. While several cone diseases have been identified exhibiting variable modes of inheritance, achromatopsia is the only one with available genetic models for investigation and will be the focus of this discussion.

A. Achromatopsia

Achromatopsia is a rare, recessive disease in which affected individuals present during infancy with nonprogressive cone dysfunction and total color blindness. As a result, patients with achromatopsia experience poor visual acuity, photophobia, and nystagmus despite a normal fundoscopic exam in most instances (Simunovic and Moore, 1998). ERGs in these patients typically show absent cone responses and preserved rod responses (Andreasson and Tornqvist, 1991).

Two types of achromatopsia are recognized: complete (typical) and incomplete (atypical). Phenotypically, the two types are similar with the only difference being that incomplete achromatopsia patients tend to retain some residual color vision and have slightly better visual acuity. To date, three genes have been linked to achromatopsia: cyclic nucleotide gated channel α3 (CNGA3), cyclic nucleotide gated channel β3 (CNGB3), and guanine nucleotide binding protein (GNAT2) (Eksandh et al, 2002; Kohl et al, 1998, 2000; Michaelides et al, 2003b; Sundin et al, 2000; Wissinger et al, 2001). Of these, only CNGA3 is associated with both types of achromatopsia (Wissinger et al, 2001).

1. Rodent models of achromatopsia

Currently, there are two mouse models of achromatopsia. The first was generated by a homozygous knockout of the α subunit of the cyclic nucleotide-gated (CNG) cation channel gene (Biel et al, 1999). Mice that are deficient in CNG3, one of the two types of CNG α subunits, exhibit progressive cone degeneration with normal rod function and structure. Photopic ERGs and oscillatory potentials in homozygous knockouts show no perceivable cone response, while rod responses were no different from wildtype mice (Lei et al, 2006). Immunohistochemistry showed that CNG3 was absent in the retina of mutant mice, and electron microscopy revealed disorganized cone outer segments.

There are two mice that exhibit cone photoreceptor function loss (cpfl) that have been proposed as models of achromatopsia. The cpfl1 mouse is caused by an autosomal recessive mutation on mouse chromosome 19 that is thought to be one of the first naturally occurring mice with cone dysfunction (Chang et al, 2002). Mice with a homozygous mutation in cpfl1 display a normal fundus and overall retinal structure with a decreased number of cones. Though ERG rod responses are normal, cone-mediated photoresponses are absent. Recently, Chang and colleagues reported a cpfl3 mouse model which is due to a mutation in the GNAT2 gene (Chang et al, 2006b). As a result, this mutation has also been called $GNAT2^{cpfl3}$. Homozygous cpfl3 mice exhibit shortening of outer segments and vacuolization over time as well as signs of early retinal degeneration (retinal vein dilation and arteriole constriction) at 8 months. ERGs show decreased photopic responses that progressively decrease with age and scotopic responses that are near normal at 9 months.

Table 3. Genetic models of retinitis pigmentosa syndromes.

Name	Gene	Protein	Modification	Species	Findings	Disease
Intracellular transport						
Bbs2$^{-/-}$	BBS2	BBS2 protein	Knockout	Mouse	Obesity, mislocalized RHO, apoptotic PR death, ONL thinning, infertility, renal cysts	BBS
Bbs4$^{-/-}$	BBS4	BBS4 protein	Knockout	Mouse	Obesity, infertility, apoptotic PR degeneration, thin ONL	BBS
MKKS$^{-/-}$ (BBS6$^{-/-}$)	MKKS	BB6 protein	Knockout	Mouse	Obesity, hypertension, increased leptin, reduced ONL, PR degeneration, abnormal social interaction, olfactory dysfunction	BBS
Structural proteins						
Ames Waltzer (av)	PCDH15	Protocadherin	Naturally-occurring	Mouse	Vestibular and auditory impairment, attenuated scotopic ERG amplitude, normal retinal architecture	USH Type IF
rd3/rd3	rd3 (USH2A)	USH2A protein	Naturally-occurring	Mouse	Progressive rod-cone degeneration with normal PR development until 2 weeks, high frequency hearing loss	USH Type IIA
shaker1 (sh1, myo7A)	Myo7A	Myosin VIIA	Naturally-occurring	Mouse	Decreased ERG, abnormal hair cell development, hearing loss	USH IB
tubby (rd5)	Tub	Tub protein	Naturally-occurring	Mouse	PR and ONL degeneration, reduced ERG, inner and outer ear hair cell loss	BBS, USH
Waltzer (v)	Cdh23	Cadherin	Naturally-occurring	Mouse	ERG abnormalities, hearing loss	USH Type ID
Ush1c216A	USH1C	Harmonin	Knock-in	Mouse	Hyperactivity, loss of Preyer reflex, circling, head-tossing	USH Type IC
Transport proteins						
Frings	Mass1	Mass1 protein	Naturally-occurrring	Mouse	Hearing impairment, audiogenic seizures, ear hair cell degeneration	USH Type IIC

Abbreviations: BBS, Bardet-Biedl Syndrome; ERG, electroretinogram; ONL, outer nuclear layer; PR, photoreceptor; RHO, Rhodopsin; USH, Usher Syndrome

2. Nonrodent models of achromatopsia

Cone degeneration has also been reported as a naturally occurring autosomal recessive disease in certain Alaskan malamutes and German shorthaired pointer dogs (Sidjanin et al, 2002). Like human achromatopsia, affected canines exhibit day-blindness and the absence of retinal cone function as tested on ERG. Linkage mapping of the canine cone degeneration (cd) disease locus identified the canine homologue of the CNGB3 gene as the positional candidate for this spontaneous retinal degeneration. A later

report by Hurn et al identified day-blindness in three other breeds of dogs: Rhodesian ridgeback cross, Chihuahua, and the Australian cattle dog (Hurn et al, 2003). Under dim light, these dogs negotiated obstacle courses successfully but became blind during daylight conditions. ERGs confirmed cone dysfunction in all three animals despite a normal ophthalmic examination. Genetic studies of the three dogs in this report have not been performed. **Table 4** summarizes the features of achromatopsia models along with the progressive cone dystrophy models (discussed below).

B. Models of progressive cone-dominant dystrophies

The phototransduction cascade is tightly regulated by proteins such as cGMP-PDE, guanylate cyclase (GC), and guanylate cyclase-activating proteins (GCAPs) (Gorcyzca et al, 1994; Haeseleer et al, 1999; Palczewski et al, 1994; Ridge et al, 2003). Specifically, GCAP is a photoreceptor-specific member of a family of Ca^{2+}-binding proteins that regulate GC activation. It is known that the mammalian retina contains two types of GC (GC1 and GC2) and two forms of GCAPs (GCAP1 and GCAP2). Recent studies have shown that GC1 and GCAP1 are essential for normal cone function and survival (Coleman et al, 2004). As a result, animal models of cone dystrophies have been developed based on these findings.

Due to the genetic proximity of GCAP1 and GCAP2, Mendez and colleagues introduced a double knockout model in which both GCAP proteins were not expressed (Mendez et al, 2001). The $Guca1a^{-/-}$ mouse (previously called $GCAP^{-/-}$) exhibits decreased flash sensitivity in darkness and delayed recovery of light responses in cones (Mendez et al, 2001; Pennesi et al, 2003). However, introduction of GCAP1 in these mice can restore the rod light response, even in the absence of GCAP2 (Howes et al, 2002).

The absence of GC1 (also known as GCE) abolishes cone cell function in mouse and chicken models as well as reducing the ERG rod response in the GC1 knockout mouse (Semple-Rowland et al, 1998; Yang et al, 1999). Knockout of GC1 in mice is accomplished by targeting the Gucy2e gene (Yang et al, 1999). Though cones are initially present at birth in affected mice, their numbers diminish fairly rapidly over time. By 5 weeks of age, cone cell bodies are unidentifiable on histology and photopic ERG measurements are barely detectable. While rods appear morphologically normal, they exhibit a paradoxical behavior in their response to light. A more recent study showed that the rate of cone cell degeneration occurred more gradually than in the initial report by Yang and colleagues (Coleman et al, 2004). In this report, cone cell loss was most severe in the inferior retina, while 40-70% of cone cells remained in the superior region after 6 months. Both GCAP1 and GCAP2 were downregulated in knockout mice, and immunostaining showed the absence of GCAP1 in the photoreceptor outer segments. Because of the link between GC1 and human Leber Congenital Amaurosis (LCA) as well as the progressive cone dystrophy seen in these animals, the GC1 knockout mouse may be a potential model of LCA (Lotery et al, 2000a; Perrault et al, 1996). The GC1 deficient chicken, also called the rd chicken, is an accepted model of LCA and is discussed below.

V. Early onset rod-cone dystrophies

A. Congenital stationary night blindness

Congenital stationary night blindness (CSNB) is the name given to a family of inherited, nonprogressive (stationary) retinal dystrophies in which affected patients experience a loss of rod-mediated (night) vision from birth but never develop the pigmentary and vascular changes associated with RP. Individuals with CSNB show signs of rod dysfunction, but rarely exhibit photoreceptor cell death. As a result, various ERG changes are seen, depending on the type and severity of CSNB. Clinically, these patients experience impaired night vision, decreased visual acuity, myopia, nystagmus, and strabismus (Tsang et al, 2007). CSNB can have an autosomal dominant, autosomal recessive, or X-linked pattern of inheritance.

Table 4. Genetic models of achromatopsia

Name	Gene	Protein	Modification	Species	Findings
Cd	CNGB3	CNGβ3 subunit	Naturally-occurring	Alaskan malamute dog, German shorthaired pointer dog	Absent ERG cone function, day-blindness
$CNG3^{-/-}$	CNG3	CNG αsubunit	Knockout	Mouse	Impaired cone function on ERG, progressive cone degeneration
cpfl3/cpfl3 ($GNAT2^{cpfl3}$)	GNAT2	Cone transducin $G_{t2}\alpha$	Naturally-occurring	Mouse	Early signs of retinal degeneration, decreased photopic ERG, progressive outer segment vacuolization
cpfl1	Unknown	Unknown	Naturally-occurring	Mouse	Progressive cone degeneration, absent ERG cone photoresponse

Abbreviations: CNG, cyclic nucleotide gated channel; ERG, electroretinogram

Oguchi's disease is the name given to a non-progressive autosomal recessive variant of CSNB that is the result of defects in rhodopsin kinase and arrestin. X-linked CSNB accounts for the majority of cases in males.

CSNB can be broadly divided into two categories based on severity: complete CSNB (CSNB1) and incomplete CSNB (CSNB2). It is hypothesized that CSNB1 is caused by mutations in the NYX gene, while mutations in CACNA1F are responsible for CSNB2 (Bech-Hansen et al, 1998; Bech-Hansen et al, 2000; Pusch et al, 2000; Strom et al, 1998; Zhang et al, 2003a). Therefore, it is believed that a number of genetic mutations can cause CSNB. Some of these include genetic abnormalities in PDE6B, rod opsin, and rhodopsin kinase (Dryja et al, 1993; Gal et al, 1994; Yamamoto et al, 1997). Particularly in the case of PDE6B, it is still a mystery why abnormalities in this rod-specific protein causes nonprogressive CSNB in some cases and progressive rod-cone degeneration in others (Danciger et al, 1995; McLaughlin et al, 1993, 1995).

1. Animal models of congenital stationary night blindness

The first reported animal model of CSNB was published in 1978 by Witzel and colleagues who described ERG abnormalities in nyctalopic Appaloosa horses that were similar to those seen in humans with CSNB (Witzel et al, 1978). However, no gene was ever identified, and this animal has had limited utility in studying CSNB due to the impracticalities of housing and handling such a large animal. Until recently, animals with mutations in Rpe65, such as the Swedish Briard dog, were thought to be useful models for CSNB (Aguirre et al, 1998). However, it was later found that these animals had progressive eye disease, which made them unsuitable for the study of stationary night blindness.

Currently, there are two primary mouse models used to study CSNB: the nob (no b-wave) mouse and a transgenic mouse carrying the H258N mutation in the gene encoding Pde6B (Pardue et al, 1998; Tsang et al, 2007). The nob mouse is a spontaneous, X-linked recessive mouse mutant that was first reported as a model of CSNB in 1998 (Pardue et al, 1998). Its name is derived from the absence of a b-wave on the ERG and decreased light sensitivity, despite normal retinal morphology on light microscopy (Pardue et al, 1998). The nob phenotype is thought to be caused by an 85-bp deletion in the mouse nyx gene, which encodes a protein of unknown function called nyctalopin (Gregg et al, 2003). Since then, a potential rat model of X-linked CSNB has been reported that has similar ERG findings to the nob mouse (Zhang et al, 2003a). However, no gene was identified. Tsang and colleagues recently developed a transgenic mouse model based on the finding that the H258N missense mutation in Pde6B was related to CSNB in a study of a Danish pedigree (Gal et al, 1994; Tsang et al, 2007). ERGs in the H258N mouse show selective loss of the b-wave with relatively normal a-waves (Tsang et al, 2007).

In 2003, Racine et al reported a potential model for CSNB in guinea pigs as a result of consanguineous mating (Racine et al, 2003). Abnormalities were seen during scotopic conditions using ERG, suggesting decreased rod function. However, cone function appeared to remain intact. Compared to rodents, which are largely nocturnal animals and have few cones in the retina, guinea pigs tend to be more diurnal (like humans). While it appears that this pedigree of animals may be a useful model for studying CSNB, no gene has been identified.

B. Leber congenital amaurosis

As its name implies, LCA is a heterogeneous autosomal recessive form of retinal degeneration that occurs in early childhood. Of all the inherited childhood retinal degenerative diseases, LCA is the earliest and the most severe (Perrault et al, 1999). Clinically, many features are seen in LCA including an extinguished ERG, pigmentary retinopathy, photophobia, central (fine) vision deterioration, fundus atrophy, and eye poking. Eventually, children with LCA develop blindness, although the majority of afflicted infants are already blind at birth. In addition, other systemic symptoms, such as cataract and keratoconus are commonly seen in these patients.

Though LCA was first described by Leber in 1869, it was not until 1995 that the first disease-causing gene, LCA1, was identified (Perrault et al, 1999). Since then, research has uncovered several genes that can cause LCA (Dejneka et al, 2003). One of the most significant genes involved in the development of LCA is RPE65 (Gu et al, 1997). It is now known that RPE65 encodes a microsomal protein in the RPE which plays a role in the metabolism of vitamin A, a precursor of rhodopsin. As a result, mutations in RPE65 lead to decreased rhodopsin production and subsequent visual impairment. Other genes implicated in LCA include (but are not limited to) photoreceptor-specific guanylate cyclase (GUCY2D), cone-rod homeobox (CRX), crumb's homolog 1 (CRB1), and the aryl-hydrocarbon interacting protein-like 1 (AIPL1) gene (Lotery et al, 2001; Perrault et al, 1996; Sohocki et al, 2000; Swaroop et al, 1999). To date, the most common single genetic cause of LCA is centrosomal protein 290 (CEP290), which accounts for approximately 21% of all cases (den Hollander et al, 2006).

1. Rodent models of Leber congenital amaurosis

As is the case with the majority of the inherited retinal degenerations, the most common animal models have been developed in mice. Soon after the discovery of the role of RPE65 in the pathogenesis of LCA, a Rpe65 knockout mouse was developed (Redmond et al, 1998). Compared to wildtype and heterozygous mice that had normal retinal morphology and ERGs, the knockout mice displayed decreased a-, b-, and c-waves on scotopic ERGs. However, photopic ERGs were preserved in all (wildtype, heterozygous, and knockout) mice, suggesting that a knockout of Rpe65 affects mostly rod function. In addition, affected mice lacked rhodopsin and 11-cis-retinal, with an over-accumulation of all-trans-retinyl esters in the RPE, which suggest that there is a block in the RPE visual cycle causing slow retinal degeneration. Light and electron microscopy show that $Rpe65^{-/-}$ mice have

shortened and disorganized outer segments with loss of photoreceptor nuclei over time.

Similar to the Rpe65 knockout mouse, the retinal degeneration 12 (rd12) mouse was recently reported as a new, spontaneously occurring mouse model of LCA that is the result of a nonsense mutation in the Rpe65 gene (Pang et al, 2005). Clinically, small, evenly spaced, white dots are seen throughout the retina, which increase with age. Rod ERGs are diminished in affected animals. Histologic abnormalities are not apparent until 6 weeks of age when disorganization of the outer segment of photoreceptor cells occurs. Eventually, lipid-like droplets accumulate in the RPE cells and the outer segment degenerates. Like the Rpe65 knockout mouse, no rhodopsin or 11-cis-retinal could be detected in the retinas of rd12/rd12 mice.

There are two mouse models of LCA that do not involve abnormalities in RPE65. The first is a homozygous knockout of Crx (Pignatelli et al, 2004). Mice that are deficient in Crx display abnormal photoreceptor development which leads eventually to a degenerative retinal morphology that is indistinguishable from the rd mouse. Specifically, outer segment morphogenesis is blocked at the elongation stage, causing failure of the phototransduction apparatus and abnormal photoreceptor synaptic endings in the outer plexiform layer (Morrow et al, 2005). Another recently developed model of LCA is the Aipl1 deficient mouse (Dyer et al, 2004; Ramamurthy et al, 2004). AIPL1 is a protein that is expressed only in the pineal gland and the retina, specifically the photoreceptors (Sohocki et al, 2000). It is now known to be chaperone involved in PDE folding (Akey et al, 2002; Pittler et al, 1995; Qin and Baehr, 1994). Mice that are deficient in Aipl1 experience normal development of the outer nuclear layer and photoreceptors, but the photoreceptors undergo rapid degeneration soon thereafter (Ramamurthy et al, 2004). Photoreceptor outer segments are shortened and disorganized, and there is loss of both rod and cone ERGs. Biochemically, it is thought that destabilization of cGMP PDE is the cause of the retinal degeneration seen in these animals.

Mutations in RPGR-interacting protein (RPGRIP) have also been linked to LCA (Gerber et al, 2001). The RPGRIP gene, also known as RPGRIP1, is expressed in photoreceptor cilia, and as its name suggests, the protein encoded by this gene interacts with RPGR to anchor it to connecting photoreceptor cilia (Hong et al, 2001). While the function of the RPGRIP protein is not completely understood, it is thought to be involved in outer segment disk morphogenesis by regulating actin (Zhao et al, 2003). In addition, RPGRIP tethers RPGR and allows it to regulate proper protein trafficking across connecting cilia. Rpgrip1$^{-/-}$ mice undergo early and rapidly progressive photoreceptor degeneration, which is clinically similar to LCA patients who experience progressive visual loss that is nearly complete by early adolescence (Pawlyk et al, 2005; Zhao et al, 2003). Photoreceptor abnormalities are seen as early as postnatal day 15, and most photoreceptors are lost by 3 months of age (Zhao et al, 2003). A recent study examining gene replacement therapy in the RPGRIP$^{-/-}$ mouse demonstrated significant morphologic and partial functional rescue of the retinal phenotype (Pawlyk et al, 2005).

The rd16 mouse has recently been implicated as a model for LCA due to its progressive and early-onset photoreceptor degeneration and ERG changes (Chang et al, 2006a). The phenotypic abnormalities in this model are due to a truncated CEP290 protein, which leads to impairment of several microtubule-based transport proteins including RPGR. As a result, affected mice develop progressive retinal thinning and decreased scotopic and photopic ERG a- and b-waves which become flat by 4 weeks of age.

2. Non-rodent models of Leber congenital amaurosis

In comparison to many other retinal degenerative diseases however, the study of LCA has an advantage in the sense that there are several higher species that can be utilized as disease models. The earliest and one of the most well-known examples is the Swedish Briard dog (Narfstrom et al, 1989; Nilsson et al, 1992; Veske et al, 1999; Wrigstad et al, 1994). These dogs have a homozygrous 4-bp deletion in Rpe65 (Veske et al, 1999). This defect is thought to cause a nonfunctional mutant protein. As a result, affected animals undergo an early onset, autosomal recessive progressive retinal dystrophy. Scotopic ERGs are either nonrecordable or of significantly decreased amplitude, while photopic ERGs are relatively preserved (Narfstrom et al, 1989; Redmond et al, 1998). Rod outer segments showed signs of early degenerative change with continued deterioration over time. Though cones were better preserved, outer segments were shortened in older animals. A lesser known canine model of LCA exists in the miniature dachshund (Curtis and Barnett, 1993; Mellersh et al, 2006). In this case, a mutation in Rpgrip1 causes a recessive cone-rod dystrophy (cord1) in affected animals (Mellersh et al, 2006). ERGs in affected animals are fairly normal early in life but become severely diminished by 9 months of age (Curtis and Barnett, 1993). At 2-3 months, there is thinning of the outer nuclear layer and degenerative changes in the rod outer segments are seen. In addition, the cone-rod dystrophy seen in this model makes it an authentic and accurate model for human LCA (Mellersh et al, 2006).

First reported in 1980, the retinal degeneration (rd) chicken is a model of autosomal recessive blindness at hatch (Cheng et al, 1980). Despite the absence of pathologic changes in the retina at the time of hatch, affected chickens fail to illicit measurable scotopic or photopic ERGs (Ulshafer et al, 1984). Beginning about 1 week after hatch, the first visible changes of degeneration are seen in the photoreceptors, first in the central retina then advancing to the peripheral retina over time. After the photoreceptors begin to degenerate, the RPE and inner retina begin to show signs of pathology. By 8 months of age, there is almost complete degeneration of the photoreceptor cell layer (Ulshafer et al, 1984; Ulshafer and Allen, 1985). Eventually, Semple-Rowland and associates were able to identify a null mutation in the chicken Gc1 gene as being responsible for the decreased levels of cGMP in the rd chicken causing retinal degeneration

(Semple-Rowland et al, 1998). As a result, the rd chicken is considered a spontaneously occurring animal model of LCA.

In the case of LCA, gene transfer therapy trials are currently ongoing and have shown great promise in reversing or at least partially ameliorating the visual defects associated with this disease. Initial results in the RPE65 null mutation dog showed improvement of functional vision after subretinal injection of a recombinant adeno-associated virus construct (rAAV.RPE65) (Acland et al, 2001; Ford et al, 2003). Gene transfer studies have also been successful in restoring visual function in the rd chicken, Gc1 knockout mouse, and the Rpe65 knockout mouse models of LCA as well (Bemelmans et al, 2006; Haire et al, 2006; Williams et al, 2006). A recently published safety study conducted in normal cynomolgus monkeys showed that treatment with rAAV.RPE65 warrants consideration for future human trials (Jacobson et al, 2006).

C. Norrie disease

Norrie disease is a congenital, X-linked recessive neurological syndrome that is characterized by bilateral, congenital blindness (Warburg, 1961, 1966). In addition, leukocoria, retinal detachment, and partial avascularity of the retina may also be seen. In later stages, the eye progressively shrinks and atrophies. A significant number of patients also suffer from hearing loss. Mental retardation and psychotic features develop in up to two-thirds of all patients (Gorlin et al, 1995). Multiple studies have identified and confirmed that a variety of mutations in the Norrie disease (NDP) gene can lead to the clinical features seen in Norrie disease (de la Chapelle et al, 1985; Donnai et al, 1988; Gal et al, 1986; Zhu et al, 1989).

1. Models of Norrie disease

Only one genetic model of Norrie disease has been reported in the literature to date. The Norrie disease mouse was created by knocking out the Ndph gene (equivalent to NDP in humans), using homologous recombination in embryonic stem cells (Berger et al, 1996). This gene encodes a protein called norrin in the cysteine knot growth factor family and is expressed in the brain and inner retina (Lenzner et al, 2002). Structurally, this protein resembles transforming growth factor-β (TGFβ), so it is thought to be involved in developmental and differentiation processes although the precise function is unknown (Meitinger et al, 1993). Hemizygous knockout of the Ndph in mice causes disorganization of the retinal ganglion cell layer and the appearance of fibrous masses within the vitreous body (Berger et al, 1996). The inner nuclear and photoreceptor cell layers exhibit regional disorganization, although it is to a lesser degree than the ganglion cell layer. Rods and cones are affected relatively late in this mouse model, but suggest nonetheless that the Ndph gene product is required for long-term photoreceptor cell survival (Lenzner et al, 2002). Malformation of the retinal vasculature occurs with persistence of hyaloid vessels in the vitreous (Richter et al, 1998). ERGs show a negative b-wave, suggesting that the inner retina is compromised (Ruether et al, 1997). In terms of non-ocular findings, inner ear pathology and hearing loss have been reported in mutant mice as well (Chen et al, 1998). Models of Norrie disease in other species have not yet been reported. **Table 5** summarizes the available models of early onset rod-cone dystrophies.

VI. Retinal tumors

In recent years, there have been numerous advancements in both the diagnosis and treatment of ocular neoplasms. Of those that occur in the posterior segment of the eye and involve the retina, retinoblastoma is the most well-documented with regard to genetic research and clinical management. Interest in this rare malignant tumor stems from that fact that retinoblastoma is the most common primary cancer of the eye in children, and it has also used as a prototypical model for inherited cancer (Gallie and Phillips, 1984).

Retinoblastoma appears as either a spontaneous, unilateral form or a hereditary, bilateral form (Zhang et al, 2004). According to Knudson's "two-hit" hypothesis of heritable disease, a mutation in both alleles of the RB1 gene leads to the manifestation of disease (Knudson, 1971). The RB1 gene, located on the long arm of chromosome 13, was the first tumor suppressor gene identified in humans (Friend et al, 1986; Lee et al, 1987) and was subsequently the first tumor suppressor gene knocked out in mice in an attempt to develop an animal model of malignancy (Clarke et al, 1992; Jacks et al, 1992; Lee et al, 1992).

Leukocoria (loss of the red reflex on fundoscopic examination) is the most common presenting sign of retinoblastoma in patients (**Figure 7**). However, it is also a late sign that is associated with poor globe salvage (Balmer et al, 2006). Strabismus is a less common sign that is typically seen earlier in the course of the disease. Though treatment in the early stages of the disease is associated with good outcomes, the prognosis for visual function and survival can be poor in the later stages.

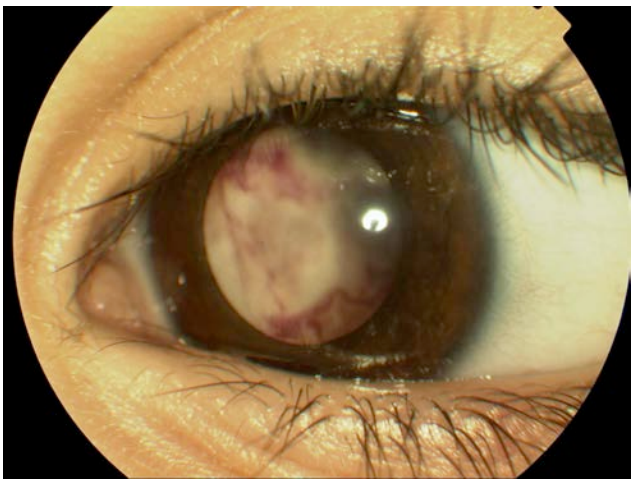

Figure 7. Photo taken from a child with leukocoria caused by retinoblastoma.

Table 5. Genetic models of early-onset retinal dystrophies

Name	Gene	Protein	Modification	Species	Findings	Disease
Transcription factors						
crx$^{-/-}$	CRX	Cone-rod otx-like homeobox transcription factor	Knockout	Mouse	Abnormal PR development, PR dendrite retraction	LCA
ND	NDP	Norrin	Knockout	Mouse	Disorganized RGC layer, late PR degeneration, fibrous masses in vitreous, retinal vessel malformation, negative ERG b-wave, hearing loss	ND
Transport proteins						
AIPL1$^{-/-}$	AIPL1	AIPL1 protein	Knockout	Mouse	Rapid PR degeneration, abnormal rod and cone ERG, Müller cell gliosis	LCA
cord1	RPGRIP	RPGR interacting protein	Naturally-occurring	Miniature dachshund	Progressively decreased ERG, ONL thinning, PR degeneration	LCA
RPGRIP$^{-/-}$	RPGRIP	RPGR interacting protein	Knockout	Mouse	Early and rapid PR degeneration, oversized outer segment discs	LCA
Visual cascade						
Briard dog	RPE65	Retinal pigment epithelium specific 65 kD protein	Naturally-occurring	Swedish Briard dog	Early-onset PR degeneration, absent scotopic ERG	LCA
rd	GC1	Photoreceptor guanylate cyclase	Naturally-occurring	Chicken	Absent scotopic and photopic ERG, progressive PR degeneration	LCA
Nob	NYX	Nyctalopin	Naturally-occurring	Mouse	Absent ERG b-wave with normal a-wave	CSNB
rd12	RPE65	Retinal pigment epithelium specific 65 kD protein	Naturally-occurring	Mouse	Decreased rod ERG, lipid accumulation in RPE cells, PR outer segment disorganization, white dots on retina, absent RHO and 11-cis-retinal	LCA
RPE65$^{-/-}$	RPE65	Retinal pigment epithelium specific 65 kD protein	Knockout	Mouse	Decreased scotopic ERG, slow PR degeneration, absent RHO and 11-cis-retinal, all-trans-retinyl ester accumulation	LCA
Others						
Nyctalopic horse	Unknown	Unknown	Naturally-occurring	Appaloosa horse	Abnormal ERG	CSNB

Abbreviations: CSNB, Congenital stationary night blindness; ERG, electroretinogram; RGC, retinal ganglion cell; LCA, Leber congenital amaurosis; ND, Norrie disease; ONL, outer nuclear layer; PDE, phosphodiesterase; PR, photoreceptor; RHO, rhodpsin; RPE, retinal pigment epithelium

B. Models of retinoblastoma

Though hereditary retinoblastoma does not occur in nonhuman species, several rodent models of retinoblastoma have been developed by transgenic methods since the discovery of RB1 (Mills et al, 1999). The first studies targeting the Rb1 gene for the purpose of developing a murine model of retinoblastoma had surprising results. Mice with a homozygous knockout of Rb1 died on day 14 or 15 of gestation. On the other hand, heterozygous Rb1 mice developed pituitary adenomas and medullary thyroid carcinomas but not ocular tumors.

The first true transgenic model of retinoblastoma was ironically the result of work targeted at developing a model of pituitary adenoma. In 1990, Windle et al reported the results of expressing a genetic construct consisting of a viral oncogene, simian virus 40 T antigen (SV40 Tag), with the promoter for the beta subunit of human luteinizing (LHbeta) hormone in mice (Windle et al, 1990). While those mice expressing high levels of LHbeta Tag in the pituitary did develop pituitary adenomas, mice that expressed LHbeta Tag in the retina developed heritable ocular tumors with histologic features similar to human retinoblastoma. Ultrastructurally, tumors in affected mice show small, hyperchromatic cells with large nuclei arranged in a rosette pattern, a finding also known as Flexner-Wintersteiner rosettes (O'Brien et al, 1989; Windle et al, 1990). Homer-Wright rosettes, consisting of a single-layered row of tumor cells surrounding a central lumen of neurofibrils, are also seen. However, it should be noted that rosette formation are nonspecific and can be found in other disruptive conditions of the retina (Johnson et al, 2007). Necrosis and local invasion of the choroid, vitreous, and optic nerve also occurs (O'Brien et al, 1990).

SV40 Tag expression can also be targeted at a specific population of intraocular cells to create tumor models using promoters for other genes besides LHbeta. One such example is interphotoreceptor retinoid binding-protein (IRBP), which is a protein that is expressed in both rod and cone photoreceptors during early retinal development (Liou et al, 1994). A transgene construct with an IRBP promotor can be used to direct Tag expression in mice causing the formation of outer retinal tumors (Al-Ubaidi et al, 1992; Howes et al, 1994; Marcus et al, 1996). Retinal tumors in these mice occur earlier than in LHbeta Tag mice and tend to be nonfocal, arising from the entire photoreceptor layer. Homer-Wright rosettes are seen in affected mice, but Flexner-Wintersteiner rosettes are not.

The role of viral oncogenes in the development of malignancy has been well-established, particularly in regard to cervical cancer. Two viral oncogenes associated with human papilloma virus-induced malignant transformation are E6 and E7 (Mills et al, 1999). Transgenic mice that express E6 and E7 in the retina under the control of an alpha-crystallin promotor are prone to develop retinoblastoma tumors that originate in the bipolar layer of the retina (Albert et al, 1994). However, the onset and prevalence of retinal tumors are highly dependent on the genetic background of these E6/E7 transgenic mice (Griep et al, 1998). As crystallin is specific to the lens of the eye, these mice also develop cataracts and lens tumors.

The first nonchimeric knockout mouse model of retinoblastoma was created in 2004 by introducing six different alleles into a single mouse strain (Zhang et al, 2004). Named after the institution where this model was developed, it has been named the St. Jude retinoblastoma mouse. Their study showed that inactivation of Rb1 and Rbl1 (also known as p107) leads to deregulated proliferation of retinal progenitor cells. Cells deficient in Rb1 and Rbl1 appear to form retinoblastoma in some animals, but these lesions may be more similar to an early stage of retinoblastoma known as "retinoma." In contrast, mice lacking Rb1, Trp53, and Rbl1 in their retinal progenitor cells developed aggressive, invasive retinoblastoma that even involved the anterior chamber.

VII. Conclusion

The identification of genetic abnormalities using animal models of retinal disease presents a unique opportunity to develop therapeutic modalities for both inherited and acquired retinal degenerative diseases that cannot otherwise be treated. Not only do models of retinal degeneration provide valuable insight into the pathogenesis of these blinding diseases, but they also serve as preclinical models for testing gene-based therapies. In addition, advances in intraocular gene transfer offer potentially new and attractive methods of retinal transgene expression that are less dependent on large scale production of high viral titers. Due to the data from such animal models, the progression from bench to bedside is already in progress. Proposals for clinical trials in early-onset retinal degeneration patients with defective RPE65 expression have already been approved (Bainbridge et al, 2006). As the medical community awaits these results and continues its efforts to identify new targets for gene transfer therapy, there is now hope that we may be able to provide effective interventions for the millions of people suffering from these most common degenerative diseases of the central nervous system in the near future.

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