

## REVIEW

# Characterization of feline hereditary retinal dystrophies using clinical, functional, structural and molecular genetic studies

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## Abstract

Only in recent years have specific mutations been elucidated for feline hereditary retinal dystrophies. Molecular genetic characterization of feline diseases has so far been a slow process but with a full genome sequence for the cat recently completed and the development of a feline single nucleotide polymorphism chip, the characterization of feline monogenic disorders will be significantly simplified. This review summarizes current knowledge with regard to specific hereditary retinal dystrophies in cats and gives an overview of how cats can be used as models in translational research.

**Key Words:** animal model, degeneration, dystrophy, feline, hereditary, retina

## INTRODUCTION

Pure-bred cats have often been considered less frequently affected by hereditary disease processes than, for example, dogs. However, the informative website Online Mendelian Inheritance of Animals (<http://omia.angis.org.au>) lists as many as 290 specific diseases with an inherited component in the cat. Further, it is only in recent years that specific mutations have been elucidated for hereditary retinal diseases of cats<sup>1,2</sup> clinically similar to those observed in the progressive retinal atrophy complex of dogs.

Reports of partial sequences (1.9X and 3X) of the cat genome<sup>3,4</sup> were important in the initial mapping and characterization of feline hereditary diseases.<sup>1,2,5</sup> With a full genome sequence (14X) completed (Wes Warren, Washington University, personal communication, 2011), as well as the development of a 75K-member single nucleotide polymorphism (SNP) chip, the mapping and characterization of feline monogenic disorders will be dependent on obtaining appropriate sample sets of nonrelated normal and affected individuals. An example is the mapping of the canine cone-rod dystrophy 3 gene (*ADAMS9*) in the Glen of Imaal Terrier breed that was recently accomplished with as few as 22 unaffected and 19 affected individuals using the canine SNP chip.<sup>6</sup> This review will summarize clinical, functional, structural and genetic characteristics with regard to two hereditary retinal disease processes in domestic felines affected by two different mutations, and discuss another two retinal dystrophies currently under investigation.

## THE *rdAc* DEFECT

The Abyssinian cat, Cinnamon (Fig. 1), the subject of the feline whole genome sequencing study, was a member of the Narfstrom pedigree<sup>7</sup> used for genetic mapping of the gene defect for *rdAc* (*retinal degeneration in Abyssinian cats*). The autosomal recessively (AR) inherited naturally occurring *rdAc* disease was first described approximately 30 years ago<sup>8,9</sup> and extensively investigated over the years as an effective animal model for human retinitis pigmentosa (RP).<sup>10–12</sup> It was only recently that the causative mutation for *rdAc* was characterized, using linkage analysis studies, candidate gene analysis, and direct sequencing of retinally expressed genes in the mapped candidate region.<sup>1</sup>

Clinically, in most homozygous (affected) cats the fundus is normal appearing until age 1.5–2 years. A slight grayish discoloration is then observed mainly in the central part of the fundus and in the far peripheral tapetal area; these changes have been designated as typical for the stage of suspected disease (stage I, S1).<sup>9</sup> With progression of the disease this discoloration becomes more extended and marked in the entire tapetal fundus, usually also with a slight vascular attenuation (stage of early disease, S2, Fig. 2). Further progression into the stage of moderately advanced disease (S3) demonstrates generalized color changes in the entire tapetal fundus together with hyper-reflectivity mainly in the midperipheral and peripheral fundus with a marked vascular attenuation. The end stage is usually reached within 2–4 years after the initial ophthalmoscopic signs of the *rdAc*

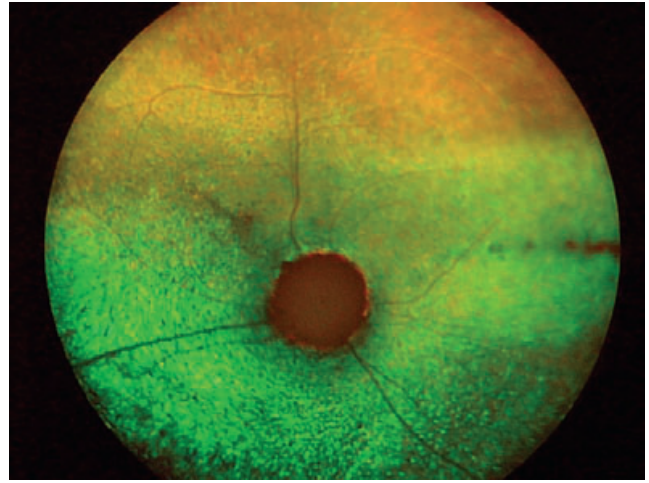


**Figure 1.** The Abyssinian cat, Cinnamon, the subject of the feline whole genome sequencing study.



**Figure 2.** Fundus of a 2-year-old Abyssinian cat with early stage (S2) *rdAc*.

defect, with a generalized atrophic fundus, hyper-reflectivity in the tapetal fundus, and with mottling and depigmented areas in the non-tapetal fundus (Fig. 3). At this advanced stage (S4) the vasculature has diminished to appear as ghost vessels observed in the most central parts. Studies regarding retinal and choroidal blood flow in the disease show that the former is severely decreased, while the choroidal microcirculation is not significantly affected by the disease process.<sup>13</sup> Further, the normal autoregulation of the retinal vasculature is still functioning even at the advanced stage of the disease.<sup>14</sup>



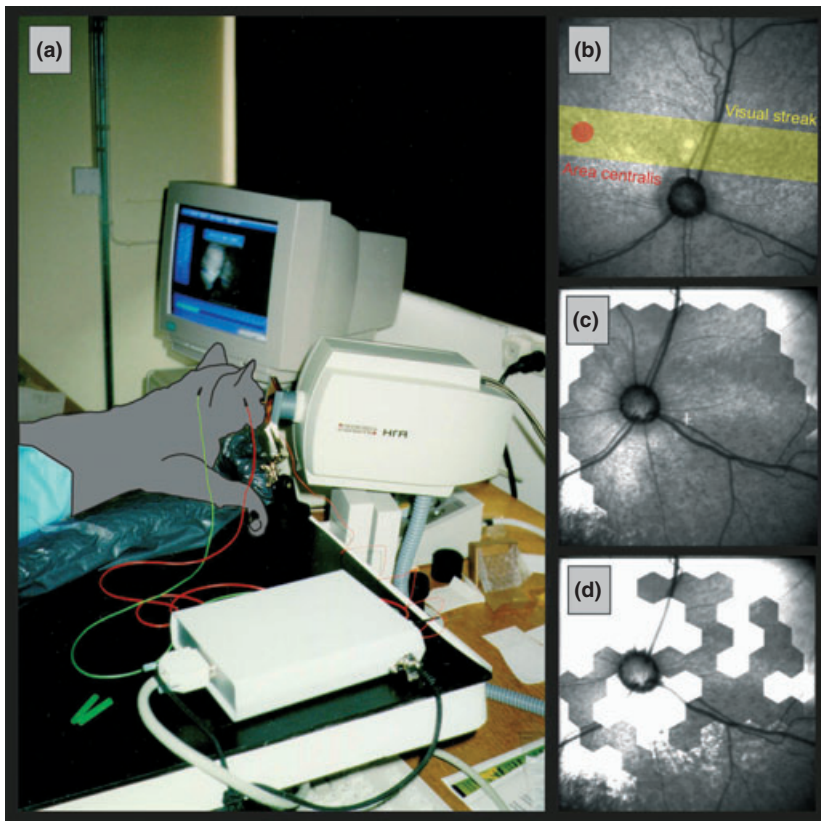
**Figure 3.** Fundus of a 6-year-old Abyssinian cat with advanced stage (S4) *rdAc*.

A series of electrophysiologic studies have been performed in affected cats at different stages of the disease process.<sup>15,16</sup> By 8 months of age, in most affected cats before ophthalmoscopic signs of the disease are prevalent, significantly reduced retinal function is demonstrated by full-field flash electroretinography (ERG).<sup>17</sup> Electroretinography a-wave amplitudes are then reduced by more than 50% compared with normal individuals,<sup>16,18</sup> with a parallel reduction in retinal oxygen tension.<sup>14</sup> Multifocal ERGs (Fig. 4) have demonstrated a generalized reduction in retinal function already at the early stage of disease (Fig. 5). At the late stage, however, there is a central sparing of the retina, as observed in human RP.<sup>12</sup>

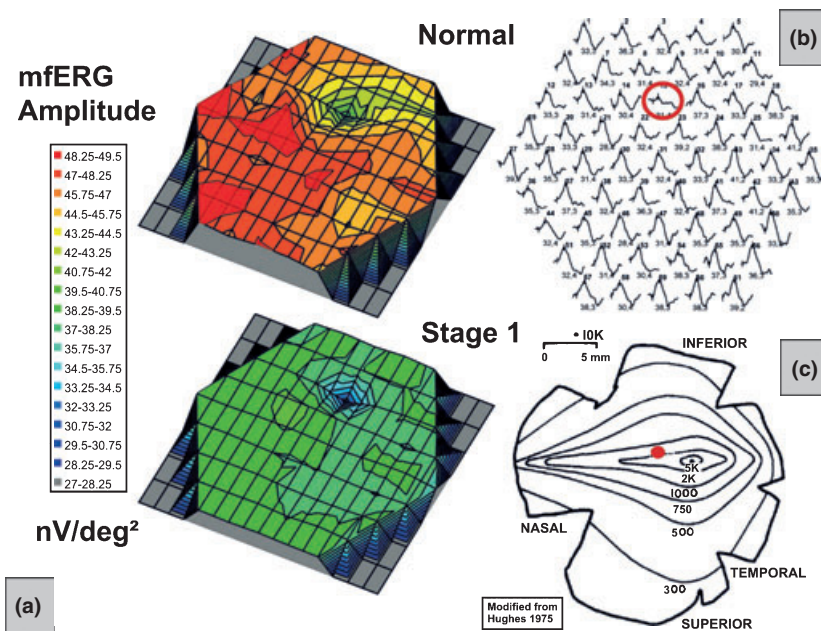
There is a degree of phenotypic variability in the *rdAc* disease. Recently it was shown that young cats could develop ophthalmoscopic signs of the *rdAc* disease already at an age of 4–5 months<sup>7</sup> and end stage blindness was reached at age 3–7 years, the latter a much more variable time point than previously described.

Rod photoreceptor outer segments exhibit the first morphological changes in individuals after the age of 5 months, observed by ultrastructure as disorganization and disruption of rod outer segment lamellar disks and the appearance of vacuoles near the photoreceptor connecting cilium.<sup>19,20</sup> Progression of the disease results in further degeneration of the rods followed by disruption also of the cone photoreceptors.<sup>21</sup> Stage 4 is characterized by complete generalized photoreceptor degeneration and subsequently retinal atrophy leading to clinical blindness.

The molecular genetic basis for *rdAc* in the *CEP290* gene<sup>1</sup> is a SNP in an intron of the felid *CEP290* gene. This generates a novel strong canonical splice-donor site, which is utilized to the exclusion of the wild type splice-donor site, resulting in a 4-bp insertion, a frame shift, and the introduction of a premature stop codon. The putative truncated CEP290 peptide would lack the more 3' KIDV and VI



**Figure 4. Recording multifocal electroretinographies (mfERGs) in cats.**<sup>12</sup> (a) Schematic set-up of a cat showing the HRA I (Heidelberg Engineering, Heidelberg, Germany) confocal scanning-laser ophthalmoscope (SLO), which in this case is used for stimulation and fundus position control. The electrical signals are picked up by a JET contact lens electrode, and the reference (red) and ground (green) needle electrodes are also visible. The fundus position is monitored during the recording session on the CRT screen to exclude movement artifacts on the results. (b) Schematic drawing of the visual streak and area centralis position on top of an SLO image. (c) Example of a multifocal electroretinography (mfERG) recording position that includes tapetal (top) and nontapetal regions (bottom). An exemplary stimulus from the pseudorandom m-sequence (d) illustrates that the light absorbance, and hence probably the light reception, will be different between tapetal and nontapetal areas, and thus it may be advocated to stimulate one of these areas at a time only.



**Figure 5. Multifocal electroretinography (mfERG) results in *rdAc* cats.** (a) Comparison of the functional topography from an *rdAc* and a normal control (modified from Seeliger and Narfström).<sup>12</sup> (b) Example of a trace array showing the blind spot (optic nerve head area, marked in red). (c) Ganglion cell density map modified from Hughes A. *The Journal of comparative neurology* 1975; **163**: 107-128. The areas of higher density correlate with a slight amplitude enhancement in the mfERG topography (a).

domains. The protein is an important component of the intraflagellar transport (IFT) system whereby specialized proteins critical for phototransduction are transferred from their site of synthesis in the inner segment of the photoreceptor, through the connecting cilium, and to the outer segment. As the rod photoreceptor disks are in a constant state

of renewal, a fully functional IFT system is critical for the maintenance of the photoreceptors.<sup>22</sup> A ciliary trafficking role for the CEP290 protein has been proposed.<sup>23</sup> Thus, CEP290 interacts with other proteins in the connecting cilium area in the normal animal and thereby maintains photoreceptor function and viability.

Cats homozygous for the *rdAc* defect are born with an ophthalmoscopically normal fundus appearance. The clinical disease that appears has a slow progression which may be one of the factors leading to the cat's exceptional ability to adapt to its, with time, decreasing retinal function,<sup>7</sup> without showing obvious signs of visual impairment. Many breed cats used for show purposes are kept in confinement indoors, often in large cages. In this environment, it is easy for cats to mask their visual impairment.

Additionally, it has recently been demonstrated that the disease mutation is widespread in a number of cat breeds; thus the *rdAc* allele is prevalent in domestic Abyssinian and Somali cats in Australia, many European countries, especially Scandinavia and UK, and in USA. Moreover, due to breeding practices including crossbreeding and the use of popular sires, the *rdAc* disease was recently discovered to be transmitted to other highly popular cat breeds as well. One such breed is the Siamese, which demonstrates a high frequency (~34%) for the *rdAc* disease allele (Table 1). It is possible to calculate the number of cats of different breeds that could be affected by *rdAc*<sup>24</sup> worldwide, based upon principles of the Hardy–Weinberg equilibrium.

#### THE *Rdy* DEFECT

An early-onset retinal dystrophy, with the gene symbol *Rdy*, was first described in a single Abyssinian cat and studied in the laboratory environment of the Animal Health Trust, UK.<sup>25</sup> A pedigree was developed and extensively studied phenotypically and by laboratory methods.<sup>26–30</sup> The disease is a primary photoreceptor disorder with an autosomal dominant (AD) mode of inheritance. The dominant allele is lethal; thus the breeding of two affected individuals results in nonviable offspring. In 2006 an affected male and an affected female were donated to the first author, who established a new pedigree of these cats for further studies. Extensive out-crossings to normal Domestic Short-haired cats were performed, resulting in 10 affected and nine unaffected kittens used for molecular genetic studies and further clinical characterization of the defect.<sup>2</sup>

Affected kittens can be differentiated from normal individuals by age 4–5 weeks: slower pupillary light reflexes and slightly dilated pupils are observed in affected kittens. By 6 weeks a pendular nystagmus may be prevalent to variable degrees. Ophthalmoscopy by age 7–8 weeks shows changes mainly in the area centralis region. There is increased mottling and a grayish discoloration is observed, which will extend peripherally within weeks. By the age of 12 weeks there is generalized hyper-reflectivity of the tapetal fundus, mottling and depigmentation of the nontapetal area and severe vascular attenuation. The disease leads rapidly to visual impairment usually observed within the first 4 months of life.

Electrophysiologically the photoreceptors never reach functional maturation. At an age of 7 weeks, the ERG demonstrates markedly reduced a- and b-waves of the scotopic

ERG, while photopic ERGs are non-recordable.<sup>2,27</sup> In the same studied individuals at 12 weeks, ERGs demonstrate unrecordable photopic responses, with scotopic responses showing a deflection (negative going wave), replacing the abnormal b-wave. The latter increases in negativity with increasing light intensity stimulation (Fig. 6).<sup>2</sup> The ERG becomes nonrecordable thereafter.

Ultrastructural studies have shown that affected individuals show abnormal and retarded photoreceptor development already at the age of 22 days as seen by electron microscopy. It has been demonstrated that neither rods nor cones develop normally. There is defective synaptogenesis with degeneration beginning in the central retinal regions and progressing toward the periphery.<sup>27,28</sup> At the time of the initial studies the disease was designated a rod–cone dysplasia, with early changes in rods and later affecting both types of photoreceptors.

Recently it was proposed that affected *Rdy* cats are affected by a cone–rod dystrophy (CoRD).<sup>2</sup> The reason for this is that the earliest ophthalmoscopic changes are observed in the area centralis region, an area of the feline retina where the concentration of cones is high in comparison with that of rods. Further, as the electrophysiological studies described above have shown that the cone system is nonfunctional at a time when there is still retinal functional activity induced by the rod system,<sup>2</sup> a fact previously also noted in the original electrophysiological studies performed in the *Rdy* cat.<sup>27</sup>

The molecular genetic basis for *Rdy* was recently elucidated.<sup>2</sup> A single base deletion in the *CRX* gene introduces a frameshift and a stop codon immediately downstream, truncating a region previously demonstrated as critical for gene function. The *CRX* gene product is critical in transcriptional activation of a number of genes involved in photoreceptor development and maintenance.<sup>31,32</sup>

A large screening of cat breeds performed in the past 2 years all over the world has failed to detect any other domestic feline breeds with the disease allele.<sup>2</sup>

#### THE BENGAL AND PERSIAN CAT RETINAL DYSTROPHIES

In the late 1960s a new feline breed, the Bengal cat, gained huge popularity. It was developed through hybridization of domestic cats and the Asian Leopard cat.<sup>33</sup> During the past years, a novel early-onset AR disorder was described in this breed.<sup>34</sup> The disease is under investigation but appears to be an early-onset primary photoreceptor disorder, leading to blindness within the first year of age. Genetic mapping and further characterization of the retinal dystrophy are in progress (D. Maggs, K. Narfström, L. A. Lyons, Manuscript in preparation, 2011).

Another feline retinal disease was described in the Persian cat breed, demonstrating an AR mode of inheritance.<sup>35</sup> Affected individuals show clinical signs of disease already at 2–3 weeks after birth and clinical blindness at approximately 16 weeks of age. Rod and cone photoreceptors in affected

**Table 1.** Frequencies observed for the rdAc genotype in 43 cat breeds and in one out-bred population

Cat breed	<i>n</i> *	Unrel†	Genotype			Frequency of <i>CEP290</i> risk allele	Anticipated frequency of affected individuals‡	Potential breed introducing <i>risk</i> allele
			<i>CEP290</i> +/ (homozygous unaffected)	<i>CEP290</i> +/- (carrier)	<i>CEP290</i> -/- (affected)			
Abyssinian/Somali (USA)§	16	16	14	2	0	0.070	0.005	
Abyssinian (UK)¶	34	34	22	10	2	0.206	0.042	
Abyssinian (Australia)¶	57	57	46	10	1	0.105	0.011	
Abyssinian/Somali (Scandinavia)¶	130	130	85	39	6	0.196	0.038	
American Curl	10	10	9	1	0	0.050	0.003	
American Wirehair	10	10	8	2	0	0.100	0.010	Siamese
Bengal	18	18	16	2	0	0.056	0.003	Siamese
Balinese/Javanese	28	24	10	12	2	0.333	0.111	Siamese
Colorpoint Shorthair	11	11	5	4	2	0.364	0.132	Siamese
Cornish Rex	20	20	19	1	0	0.025	0.001	Siamese
Munchkin	15	15	14	1	0	0.033	0.001	
Ocicat	18	18	15	3	0	0.083	0.007	Siamese/ Abyssinian
Oriental Shorthair	46	25	11	11	3	0.340	0.116	Siamese/ Abyssinian
Siamese	91	49	28	16	5	0.265	0.070	
Singapura	6	6	5	0	1	0.167	0.028	
Tonkinese	7	7	6	1	0	0.071	0.005	Siamese
American Shorthair	9	9	9	0	0	0.000	0.000	
Angora	13	13	13	0	0	0.000	0.000	
Birman	10	10	10	0	0	0.000	0.000	
Bobtail	13	13	13	0	0	0.000	0.000	
Bombay	9	9	9	0	0	0.000	0.000	
British Shorthair	9	9	9	0	0	0.000	0.000	
Burmese	35	35	35	0	0	0.000	0.000	
Chartreux	10	10	10	0	0	0.000	0.000	
Devon Rex	20	20	20	0	0	0.000	0.000	
Egyptian Mau	19	19	19	0	0	0.000	0.000	
Exotic	18	18	18	0	0	0.000	0.000	
Havana	8	8	8	0	0	0.000	0.000	
Himalayan	17	17	17	0	0	0.000	0.000	
Korat	7	7	7	0	0	0.000	0.000	
Maine Coon cat	13	13	13	0	0	0.000	0.000	
Manx	19	19	19	0	0	0.000	0.000	
Norwegian Forest cat	19	19	19	0	0	0.000	0.000	
Persian	19	19	19	0	0	0.000	0.000	
Ragdoll	8	8	8	0	0	0.000	0.000	
Russian Blue	10	10	10	0	0	0.000	0.000	
Scottish Fold	20	20	20	0	0	0.000	0.000	
Selkirk Rex	20	20	20	0	0	0.000	0.000	
Siamese ('Appleheads')	31	18	18	0	0	0.000	0.000	
Sphynx	20	20	20	0	0	0.000	0.000	
Tennessee Rex	19	19	19	0	0	0.000	0.000	
Thai	2	2	2	0	0	0.000	0.000	
Turkish Angora	14	14	14	0	0	0.000	0.000	
Turkish Van	9	9	9	0	0	0.000	0.000	
Outbred (USA)	92	92	90	2	0	0.011	0.000	
Total cats this study (North America)	792							
European samples								
Balinese	1		0	0	1	1.000	1.000	
Bengal	2		2	0	0	0.000	0.000	
Ocicat	3		1	2	0	0.333	0.111	
Oriental Shorthair	12		7	4	1	0.250	0.063	
Peterbald	8		2	4	2	0.500	0.250	Siamese
Siamese	28		18	9	1	0.196	0.039	
Total European	54							
Total cats	846							

Reprinted from Menotti-Raymond *et al.*<sup>24</sup>.

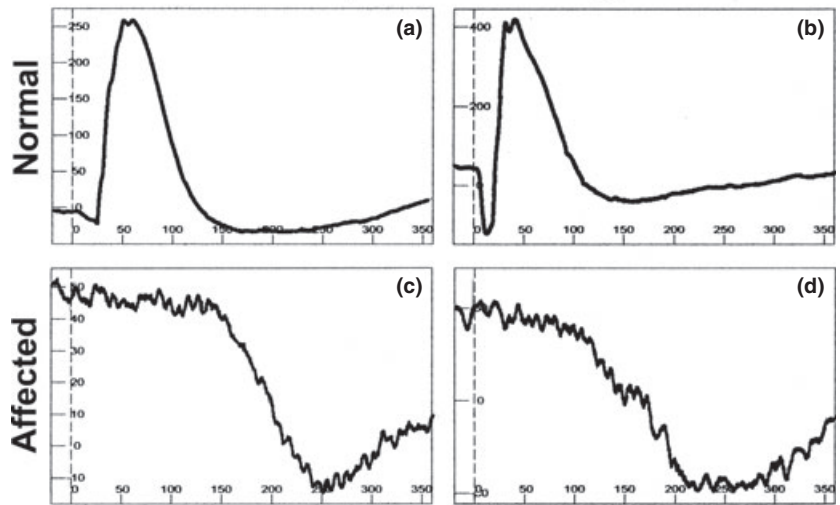
\*numbers of individuals include cats in this study, only.

†total number of unrelated cats used for statistical analyses.

‡estimates are based on expectations for populations in Hardy–Weinberg equilibrium.

§Menotti-Raymond *et al.*<sup>1</sup>¶Narfström *et al.*<sup>7</sup>

## Scotopic recordings



**Figure 6.** Representative electroretinography (ERG) responses (part of an extended protocol) obtained in similar dark-adapted conditions in a normal and an *Rdy*-affected litter-mate, age 11 weeks, under medetomidine/ketamine anesthesia, and using the HM sERG (RetVetCorp, Columbia, MO, USA). Recordings using two light intensities of white light in the dark-adapted state (300 mcd.s/m<sup>2</sup> [a, c] and 3000 mcd.s/m<sup>2</sup> [b, d], respectively) are demonstrated. Rod-induced ERG responses are shown with negative recordings induced by the rod photoreceptor system. These responses were obtained when cone responses were abolished or nonrecordable.

individuals never reach full maturity. Retinal degenerative changes are limited to the photoreceptor layer, the outer plexiform layer, and the retinal pigment epithelium while the inner retina is normal appearing until late in the disease process. The molecular genetic defects for the Bengal and Persian cat retinal dystrophies, respectively, have not yet been elucidated.

### CATS AS MODELS FOR HUMAN RETINAL BLINDING DISEASE

In humans, mutations in the *CRX* gene are associated with human AD CoRD, and both AD and AR Leber's congenital amaurosis (LCA).<sup>36</sup> The *Rdy* cat is the first large animal model for *CRX*-linked spontaneous retinal disease. Mutations in the *CEP290* gene have been reported in RP, LCA as well as in the syndromic retinopathies: Joubert, Meckel-Gruber and Bardet-Biedl.<sup>37–39</sup> Research, utilizing large animal models is the natural step forward with regard to the treatment of these devastating diseases. The importance of such work was actually shown using another large animal model for retinal blinding disease: the *RPE65* null mutation dog. First, initial careful characterization of the retinal disease process was performed,<sup>40–43</sup> followed by therapeutic intervention using gene therapy with proof of principle showing that gene therapy can actually lead to improvement of retinal function and structure.<sup>44,45</sup> Similar intervention was thereafter performed in human patients leading to successful restoration of vision.<sup>46,47</sup> Thus, Abyssinians, Siamese, and other breeds of cats with the *rdAc* defect and mixed-breed cats with the *CRX* mutation are candidates for future translational research. This will focus on treatment modalities with regard to human retinal ciliopathies and early-onset photoreceptor dysplasias as there now are comparable spontaneous animal models for both groups of diseases.

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