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VIEWPOINT

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Consensus guidelines for nomenclature of companion animal inherited retinal disorders

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Abstract

Companion animals, namely dogs, cats, and horses, can be affected with many forms of hereditary retinal disease. The number of such diseases characterized in the last decade has increased substantially, and nomenclature is nonstandardized, heterogenous, and confusing. We provide in this viewpoint article consensus guidelines for naming of companion animal hereditary retinal diseases, either prospectively or retrospectively. These consensus guidelines have been developed with the purpose of standardizing nomenclature. We provide examples for the iterative nomenclature process and a comprehensive File S1 on proposed renaming of previously described diseases.

KEYWORDS

breed, dog, genetic, hereditary, naming, progressive retinal atrophy

The number of genes and mutations identified as being associated with hereditary retinal diseases in companion animals and people increases every year. As of December 2023, mutations in 43 genes have been associated with retinal disorders in dogs, 5 genes in cats, and 3 genes in horses. A brief synopsis of genes associated with retinal disorders in dogs is provided in Table 1, and cats, and horses are provided in Table 2.

Companion animals, particularly cats and dogs have been studied extensively as many genes causative for retinal

TABLE 1 Mapped genes associated with inherited retinal disorders in dogs. **RPGRIP1* has 2 or more modifiers that affect disease onset and/or progression.

Gene	Phenotype (acronym, brief description if IRD)
ABCA4	IRD; Late-onset, discoloration of area centralis/visual streak and more widespread in late stages
ADAM9	PRA
BBS2	PRA
BBS4	IRD; limited clinical description of progression
BEST1	IRD; canine multifocal retinopathy
CaBP4	PRA
CCDC66	PRA
CNGA1	PRA
CNGA3	ACH
CNGB1	PRA
CNGB3	ACH
COL9A2	DYSP (worse severity in homozygous mutant)
COL9A3	DYSP (worse severity in homozygous mutant)
FAM161A	PRA
GUCY2D	PRA
IFT122	PRA
IMPG2	PRA
JPH2	IRD; limited clinical description of progression
LRIT3	SNB
MERTK	IRD; multifocal discoloration and degeneration
MIA3	IRD; limited clinical description of progression
NDP	MOD
NECAP1	PRA
NHEJ1	CEA
NPHP4	PRA
NPHP5(IQCB1)	PRA
PCARE	IRD; limited clinical description of progression
PDE6A	PRA
PDE6B	PRA
PPT1	PRA
PRCD	PRA
RAB3GAP1	MOD
RBP4	MOD
RD3	PRA
RHO	ADPRA
RPE65	IRD; early area centralis degeneration with very slow/minimal generalized retinal atrophy in some descriptions
RPGR	XLPRA
*RPGRIP1**	PRA
MAP9, L3	Not applicable (modifiers for *RPGRIP1* PRA)
SAG	PRA
SIX6	MOD
SLC4A3	PRA
STK38L	PRA
TTC8	PRA

disorders are shared with humans,[1–6] and animals have provided an integral translational platform upon which to study genotype–phenotype associations, natural history of disease, and the impact of therapeutic interventions. A recent success story is the Briard breed of dog that in the 1990s was identified to harbor a retinal disease-causing mutation in *RPE65*,[7] and subsequently contributed extensively to the translation of *RPE65* retinal gene augmentation therapy into humans,[8–10] This therapy is now commercialized after approval by regulatory agencies in the United States and Europe. By selective breeding practices, the causative mutation has been significantly reduced in frequency, whereby the allele frequency of the *RPE65* mutation overall in companion dogs is now estimated to be <0.0001.[11]

In the interim period from initial retinal disease identification to causative gene discovery, many forms of hereditary retinal disease in dogs have been named by their respective investigators, with a resultant plethora of acronyms and names attributed to diseases. Occasionally, descriptive names were initially attributed to a disease before the full natural history was elucidated, therefore some commonly used names incorrectly describe the phenotype. For example, dogs with an *RPE65* mutation were initially classified as having a congenital stationary night blindness (CSNB) whereas subsequent phenotyping showed the condition did progress and involved more than rod-mediated night vision. The naming process thus far has not been conducted under any specific guidelines for nomenclature. Now that there are many diseases and known associated genes, there is a growing need and consensus to create a logical, standardized method to name each new disease correctly as phenotype and genotype are clarified. This standardized naming approach can also be applied retrospectively, to rename previously described conditions for consistency. In this viewpoint article, we set out consensus guidelines for the naming of hereditary retinal diseases in companion animals, based on

TABLE 2 Mapped genes associated with inherited retinal disorders in cats and horses.

Gene	Phenotype (acronym, brief description if IRD)
Cat	
AIPL1	PRA
CEP290	PRA
CRX	ADPRA
KIF3B	PRA
RDH5	IRD; slow dark adaptation. discoloration and degeneration of area centralis and visual streak
Horse	
GRM6	IRD; single case report with 4–5 year history of night vision deficit and negative ERG OU
PMEL	MOD
TRPM1	SNB

the level of characterization of phenotype and genotype. We provide as Supplementary information, an extensively researched table of the current status of hereditary retinal disorders, outlining how we propose to (re)name each disorder.

Hereditary diseases of the retina fall into three main subsets: (1) progressive, (2) nonprogressive, and (3) either idiosyncratic, affecting more than one ocular site, or syndromic (affecting other body sites). Most conditions are inherited in an autosomal recessive manner, whereby an animal must possess two copies of the mutant gene to have the disease. A small number of conditions are inherited in a dominant inheritance pattern, whereby one copy of the mutant gene is sufficient to cause disease, although incomplete penetrance may affect the severity of the condition in heterozygous mutant carriers. Sex-linked inheritance is uncommon, whereby the X chromosome contains the mutant gene, and males are more commonly affected than females. Other, more complex modes of inheritance are rarely described but one example is maternal inheritance described for multiple ocular defects (MOD) in dogs due to a mutation in the *RBP4* gene.[12] We propose naming of inherited retinal diseases (IRDs) based on phenotype, breed, and genotype (when characterized). Conditions of the cornea and lens, glaucoma, and lysosomal storage diseases are not included in these naming guidelines, because these conditions are either already consistently named or contain fewer diseases. These other heritable ocular conditions could also be named (or renamed) using our retinal disease nomenclature guidelines. A summary table of proposed nomenclature acronyms is outlined in Table 3. The following sections address naming of diseases in detail.

1 | SUGGESTED NOMENCLATURE OF DISEASES

Here we provide recommendations for naming of diseases, depending on the level of characterization that has been reported/performed and the type of disease identified. Diseases previously described should be allocated nomenclature according to phenotype and genetic etiology. If further phenotypic or genetic characterization is performed following initial description of the condition, a condition can be "renamed" using these guidelines. A comprehensive list of proposed names for previously characterized conditions is provided in File S1.

A **IRD-breed**: If a disease is heritable in nature (confirmed by pedigree analysis, test breeding, etc.), but the course of disease is not clear based on the available clinical information, it should be conservatively named until further studies are done. Nomenclature includes the acronym for inherited retinal disease (IRD), followed by the breed of animal it is described in. Multiple breeds can be described, and if the original report is derived from a mixed-breed population, "mixed-breed" can be used as proxy of the breed. If more than one IRD is present within one breed (without progression to items B-G), they can be numerically identified.
Example: A new form of hereditary retinal disease has been identified in the Brittany breed of dog by pedigree analysis, but the natural history is unclear. Recommended nomenclature: IRD-Brittany. If >1 IRD is present in the breed, they would be named IRD1-Brittany IRD2-Brittany etc.

B **PRA (or SB)-breed:** If there is sufficient evidence that a retinal disease is both heritable and progressive in nature with broad retinal atrophy (i.e., evidence of bilateral and reasonably symmetrical progressive tapetal hyper reflectivity; generalized retinal thinning shown by histology or OCT with progressive retinal functional deficits as assessed by electroretinography), it is (re) classified as a progressive retinal atrophy (PRA). If stationary (nonprogressive in nature), it is (re)named as a stationary blindness (SB). Some conditions may not fit into either of these categories (see D. below).

TABLE 3 Acronyms and guidelines for application for heritable retinal diseases.

	Category	Subcategory	Phene acronym
Inheritance pattern	Unknown or autosomal recessive	NA	None
	Autosomal dominant (high penetrance)	NA	AD
	X-Linked	NA	XL
Progression	Unknown but inherited (inherited retinal disorder)	NA	IRD
	Stationary blindness – heritable vision changes but nonprogressive	NA	SB
		Cone pathway dysfunction (achromatopsia)	ACH
		Rod pathway dysfunction (stationary night blindness)	SNB
	Heritable, progressive, diffuse, bilateral, and relatively symmetrical	NA	PRA
Idiosyncratic, syndromic, or affecting multiple ophthalmic sites	Collie Eye Anomaly	NA	CEA
	Multiple Ocular Defects (involving the retina)	NA	MOD
	Retinal dysplasia	NA	DYSP

Example 1: A hereditary retinal disease in the Brittany breed is progressive. Recommended nomenclature: PRA-Brittany.

Example 2: A hereditary retinal disease in the Brittany breed is nonprogressive.

Recommended nomenclature: SB-Brittany.

C **ACH (or SNB)-breed:** In cases of heritable conditions with photoreceptor dysfunction but minimal to no progressive degeneration, diseases are (re)classified as a cone dysfunction (achromatopsia, ACH) or a rod dysfunction (stationary night blindness SNB).

Example: Nonprogressive heritable retinal disease in the Brittany shows rod dysfunction with minimal cone dysfunction by electroretinogram. Recommended nomenclature: SNB-Brittany.

Note: The authors carefully considered the option of within the broad category of PRA, recommended nomenclature that includes designation of cone-rod degeneration or rod-cone degeneration, to further delineate which photoreceptor subtype is affected earlier in disease. This is an area which, in the past has been subject to incorrect designation. In addition, correct designation relies on the investigator performing studies on animals that align with the timing of onset of disease of each photoreceptor subtype. This is not always feasible, particularly if degeneration is rapid, or early onset. Whilst this designation will not form part of the disease name, investigators are encouraged to describe this detail within manuscripts, as this information has clinical, research, and translational relevance.

D **IRD (or CEA or MOD or DYSP)-breed:** Phenotypes that do not manifest in the typical types described above either remain as an IRD (for example canine multifocal retinopathy) or have specific acronyms assigned: CEA (Collie Eye Anomaly), MOD (Multiple Ocular Defects that also involve the retina), DYSP (dysplasia)

E **XLPRA or ADPRA-breed:** If pedigree information strongly supports an X-linked mode of inheritance, the prefix XL can be added. If autosomal dominant (with evidence of complete penetrance), the prefix AD can be added. Because most diseases are autosomal recessive in nature, no prefix will be added if an autosomal recessive inheritance pattern is suspected or confirmed.

Example 1: A heritable retinal disorder showing X-linked inheritance with uncertain progression in the Brittany. Recommended nomenclature: XLIRD-Brittany.

Example 2: A heritable retinal disorder showing X-linked inheritance with progressive retinal atrophy in the Brittany. Recommended nomenclature: XLPRA-Brittany.

F **Phene-*gene*-breed:** Once a gene is definitively associated with a disease, with adequate evidence of causation, the name of the disease phenotype can also incorporate the gene (which is italicized). The name does not include the variant description as this would be overly cumbersome, However, authors of manuscripts describing IRDs in which phenotype and genotype are known, and the exact variant is critical should

refer to the variant ID ([1]OMIA or other) in the manuscript.
Example: For PRA that has been definitively associated with a mutation in *PRCD* in the Brittany breed of dog, the name would be PRA-*PRCD*-Brittany.

G **Inclusion of the historical name if previously described:** This is highly recommended; at the authors' discretion, the old/familiar name of the condition could be included in parentheses after the nomenclature.
Example: Oculoskeletal dysplasia (previously named osd2) in the Samoyed, now associated with a mutation in the gene *COL9A2*. Recommended nomenclature: DYSP-*COL9A2*-Samoyed (osd2).

AUTHOR CONTRIBUTIONS

Freya M. Mowat: Conceptualization; data curation; investigation; methodology; project administration; writing – original draft; writing – review and editing. **Simone Iwabe:** Conceptualization; data curation; investigation; methodology; writing – review and editing. **Gustavo Aguirre:** Conceptualization; methodology; writing – review and editing. **Simon Petersen-Jones:** Conceptualization; methodology; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts to disclose.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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