Human Genetics (2019) 138:441–453
https://doi.org/10.1007/s00439-019-01999-6

REVIEW

Natural models for retinitis pigmentosa: progressive retinal atrophy in dog breeds

Morgane Bunel[1] · Gilles Chaudieu[2] · Christian Hamel[3] · Laetitia Lagoutte[1] · Gaël Manes[3] · Nadine Botherel[1] · Philippe Brabet[3] · Philippe Pilorge[4] · Catherine André[1] · Pascale Quignon[1]

Received: 21 December 2018 / Accepted: 14 March 2019 / Published online: 23 March 2019

Abstract
Retinitis pigmentosa (RP) is a heterogeneous group of inherited retinal disorders eventually leading to blindness with different ages of onset, progression and severity. Human RP, first characterized by the progressive degeneration of rod photoreceptor cells, shows high genetic heterogeneity with more than 90 genes identified. However, about one-third of patients have no known genetic causes. Interestingly, dogs are also severely affected by similar diseases, called progressive retinal atrophy (PRA). Indeed, RP and PRA have comparable clinical signs, physiopathology and outcomes, similar diagnosis methods and most often, orthologous genes are involved. The many different dog PRAs often segregate in specific breeds. Indeed, undesired alleles have been selected and amplified through drastic selection and excessive use of inbreeding. Out of the 400 breeds, nearly 100 have an inherited form of PRA, which are natural animal models that can be used to investigate the genetics, disease progression and therapies in dogs for the benefit of both dogs and humans. Recent knowledge on the canine genome and access to new genotyping and sequencing technologies now efficiently allows the identification of mutations involved in canine genetic diseases. To date, PRA genes identified in dog breeds correspond to the same genes in humans and represent relevant RP models, and new genes found in dogs represent good candidate for still unknown human RP. We present here a review of the main advantages of the dog models for human RP with the genes already identified and an X-linked PRA in the Border collie as a model for orphan X-linked RPs in human.

Dog as a powerful model for the study of human genetic diseases

Intra-breed homogeneity and interbreed heterogeneity

The domestic dog, *Canis lupus familiaris* is the first domesticated animal and the most adapted to communicate with humans (Galibert et al. 2011). No other species present such a large range of phenotypic diversity of size, morphology, coat colours, ability to work, guard, hunt… Indeed, dogs have been bred by humans for thousands of years, according to specific morphological and behavioural features. In the nineteenth century, breed standards have even been written so that drastic artificial selection has been applied to perfectly correspond to standards. As a consequence, dog breeds are genetic isolates, comparable to human sub-populations isolated through religion, social specificities, and geographical constraints. The dog species thus shows an amazing intra-breed homogeneity and inter-breed heterogeneity. Currently, more than 400 breeds are listed, described and recognized by different organizations such as the "Fédération Cynologique Internationale" (FCI) and the American Kennel Club (AKC), with definite breed standards.

Dog genetic diseases

The artificial selection with selective pressure, inbreeding, use of popular sire for reproduction, to maintain phenotypical and behavioural features led to a drastic reduction of the genetic diversity within each breed. Indeed, alleles

✉ Pascale Quignon
pascale.quignon@univ-rennes1.fr

1 University of Rennes, CNRS, IGDR (Institut de génétique et développement de Rennes)-UMR6290, 35000 Rennes, France

2 Clinique Vétérinaire, 52 Boulevard M. Pourchon, Clermont-Ferrand 63100, France

3 INSERM U1051, Institute for Neurosciences of Montpellier, Hopital Saint Eloi, Montpellier, France

4 Clinique vétérinaire Rive Ouest, Rennes, France

responsible for desired traits have been selected and accumulated as well as undesired alleles close to the selected alleles. Thus diseases are, for most of them, breed specific and nearly all breeds suffer from one or several hereditary diseases. Interestingly, some of these diseases are clinically similar to human diseases with the same gene involved in dogs and humans. For instance in dermatology, a mutation in the *PNPLA1* gene is responsible for ichthyosis in the Golden retriever breed and mutations in the same gene were found to be responsible for ARCI (Autosomal Recessive Congenital Ichthyosis) in humans (Grall et al. 2012). This is also the case for the *KRT16* gene involved in a rare keratoderma in both Dogue de Bordeaux and humans (Plassais et al. 2014). Similarly genes implicated in dog and human common retinopathies, neurological, cardiac, renal, and other genetic diseases, are easier to identify in genetic isolates such as dog breeds, than in the general mixed human population. Indeed, the prevalence can be very high, with up to 30% of individuals affected by a given disease in a given breed, as for example ichthyosis in Golden retriever (Grall et al. 2012). In fact, these diseases, spontaneously occurring in dogs with high frequency in certain breeds, often correspond to rare diseases in humans for which the implicated genes and mutations are difficult to track because these mutations are generally present in sporadic cases or in one or few human families. In addition, contrary to other animal models, such as rodents in which diseases are mostly chemically or genetically induced, dogs naturally develop the diseases, in a shorter period of time compared to humans, the life span of a dog being between 10 and 14 years. Moreover, in developed countries, dogs have the best medical follow-up after humans. Dog's life expectancy, reproduction rate and number of dogs per litter allow to have access to many individuals and to pedigrees registered by kennels.

In this context, the "Canine Genetics" team (IGDR, Rennes) created and manage a biological resource centre of canine samples, Cani-DNA CRB (http://dog-genetics.genouest.org), implemented by samples collected by a large veterinary network. Through this biobank, blood and tissue samples from affected and unaffected dogs are being collected for genetic studies. The samples come with clinical information, diagnosis and clinical follow-up as well as the dog pedigree. As in human genetic research, these samples and data constitute genetic resources to perform genetic linkage studies, genome wide association studies (GWAS), sequencing… Moreover, the mode of inheritance of diseases can be hypothesized owing to pedigree data collected over a short period of time with many generations (Fig. 1). The dog is also a powerful model to investigate the role of the "environment" in the disease onset, progression, severity and outcome, since we share with our pets the same environment: our settlement and our habits and life exposures (for instance, pollution, sun, toxins exposure and diet).

To conclude, the study of canine genetic diseases in predisposed dog breeds can unravel new genes and new pathways more easily than in humans, and then provide not only candidate genes to screen human patients, but also natural models for therapies, for a double benefit in human and canine medicine. The canine model helps to unravel the genetics of homologous diseases, their pathophysiology and their treatments, up to clinical trials that can be settled in dogs prior to humans. We can cite for example, research on gene therapy performed on retinal diseases (Acland et al. 2005; Aguirre et al. 2007; Beltran et al. 2014; Pichard et al. 2016), or cell therapy on muscular diseases (Rouger et al. 2011; Lorant et al. 2018). Concerning retinal diseases, one of the most known dog model is the Briard RPE65 model. Indeed, mutations in the RPE65 gene have been described as responsible of Leber's congenital amaurosis in human and congenital stationary night blindness in dog. In 2001, Acland et al. showed that a subretinal injection of a recombinant adeno-associated virus carrying a wild-type *RPE65* lead to a significant improvement in retinal function, assessed by ERG, and improvement of the vision assessed by an obstacle course test (Acland et al. 2001). Furthermore, responses remained stable in dogs followed electroretinographically for 3 years. More recent works on gene therapy are being performed for several known mutated genes, such as *PDE6A, PDE6B, RHO, RPGR, RPGRIP1, CNGB3, BEST1* (Petersen-Jones and Komáromy 2015).

Human retinitis pigmentosa (RP) and dog progressive retinal atrophy (PRA)

Among inherited human retinal diseases, 50% are pigmentary retinopathies called Retinitis pigmentosa (RP) (Daiger et al. 2013). They compose a heterogeneous group of disorders characterized by a progressive loss of vision and they are leading to blindness because of the degeneration of the photoreceptor cells of the retina. As humans, dogs are affected with such retinopathies called progressive retinal atrophies (PRA) in veterinary medicine which are clinically and genetically similar to human retinitis pigmentosa.

Human RP are classified according to their syndromic or non syndromic nature and their mode of inheritance. Syndromic RP include for example the Usher syndrome that associates RP with deafness or the Bardet Biedl syndrome, which comprises a RP, obesity, intellectual disability and/or renal disorders. Concerning the non syndromic RP, all modes of inheritance are described: autosomal recessive, autosomal dominant and X-linked. Non syndromic RP represent 70 to 80% of all RP (Verbakel et al. 2018) and are also called rod-cone dystrophies (RCD). Indeed, RP are characterized by a primary degeneration of rod photoreceptors followed by a secondary degeneration of cones, as in dog

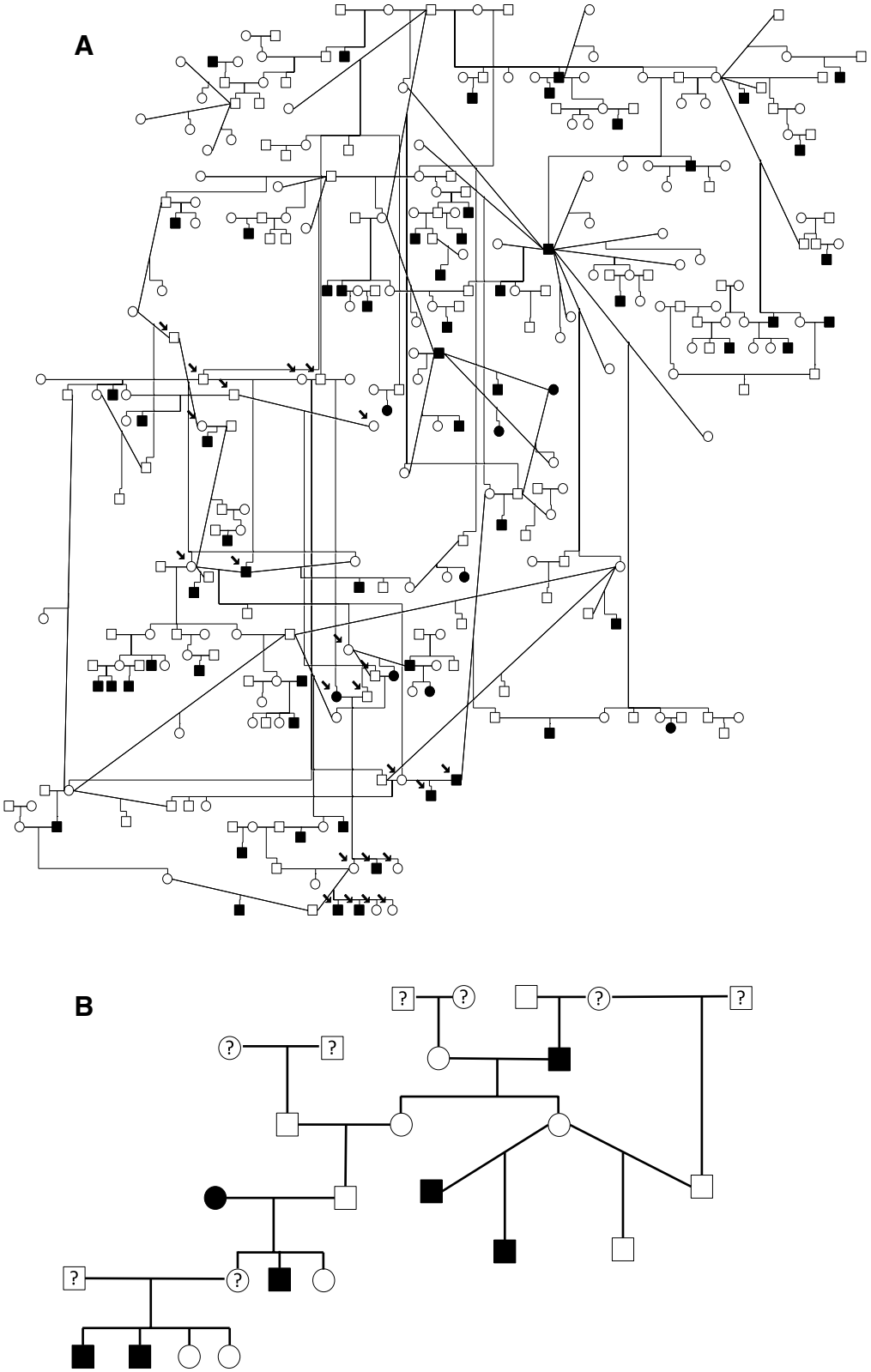

Fig. 1 Border collie pedigrees. **a** Pedigree of 312 Border collies. **b** Zoom in on the Border collie pedigree used in genetic analyses. In the Border collie breed, the disease most probably segregates as X-linked recessive since unaffected parents produce affected dogs, and most affected dogs are males. Circles represent females, squares represent males. Affected and unaffected dogs are noted with empty and black symbols, respectively. Dogs indicated with an arrow in **a** were used to make the **b** part. In **b**, question mark indicates that no clinical data are available

PRA. Although RP remain rare diseases, they are the most frequent forms of retinal degenerations with a worldwide prevalence of approximately 1:4000 (Pagon 1988).

All human non syndromic RP have similar clinical features but the genetic causes are different, even from one family to another. To date, over ninety genes and loci are associated with RP but there are still human patients with no genetic diagnosis. For example 40% of Spanish families in which segregate an autosomal dominant RP are not genetically solved (Martin-Merida et al. 2018). Due to the genetic heterogeneity of these diseases, finding the implicated genes and causative mutations remains a challenge in human genetics. Thus, models spontaneously developing retinopathies, clinically similar to RP are an invaluable opportunity for the genetics, physiopathology and treatments of human RP.

Dog PRA can serve as natural models for human RP. Indeed, the similarities between canine PRA and human RP have been described since the beginning of 1900s, first in the Gordon Setter breed (Magnusson 1911; Pary 1953). But it is only in the late 1980s that the first gene implicated in PRA, *PDE6B*, could be discovered in the Irish Setter breed, with a non-sense mutation in exon 21 (Suber et al. 1993). Interestingly, this gene is known to be implicated in the RP40 form in human (McLaughlin et al. 1993). This first finding was followed by numerous discoveries of homologous genes involved in both canine and human retinopathies.

In the dog species, more than 100 breeds are known to be affected with different PRA forms (Petersen-Jones 1998, 2005; Patterson 2000; Aguirre and Acland 2006). PRA are usually classified according to the age (early and late onset PRA) and the dog breed. The prevalence of the disease varies depending on the breeds and even on the geographic origin of the breed. Indeed, some breeds have a high frequency of affected individuals such as Poodles, Retrievers, Spaniels and Border collie, around 8% of the population being affected in the latter breed (Chaudieu et al. 2014), and other breeds can show sporadic cases such as Welsh Terrier, or Puli (Chaudieu and Chahory 2013). Due to breeding practices, dog breeds are mainly affected by only one form of PRA suggesting a unique genetic cause but some breeds can be affected by several forms (Table 1; Fig. 2). For example, Golden retrievers are affected by an early onset PRA form and a late onset form, for which three genes have been identified to date: *PRCD* (photoreceptor disc component) *SLC4A3* (solute carrier family 4 member 3) and *TTC8* (tetratricopeptide repeat domain 8) (Zangerl et al. 2006; Downs et al. 2011, 2014). However, it is estimated that around 9% of PRA cases in the Golden Retriever still remain unexplained (Downs et al. 2014). On the other hand, some frequent mutations are the cause of the disease in several breeds: an extreme situation is observed for the *PRCD* gene with a unique mutation affecting over 18 breeds, indicating an ancient founder effect of this mutation (Zangerl et al. 2006; Goldstein et al. 2006) (Table 1).

Clinical displays and diagnosis of canine PRA and human RP

Functional signs

The first symptom of PRA/RP is a night blindness. Affected people and dogs have then to deal with a loss of peripheral vision inducing a reduced visual field with tunnel vision for advanced forms, a poor perception of contrasts and movements. In humans, with the progression of the disease, a photophobia and a loss of the visual acuity (reduction of the cones sensitivity) appear gradually with difficulties to perceive colors, and in the most severe cases, the ultimate stage of the disease is a complete blindness that settles, in humans, later in life (Hamel 2006). Humans can easily express their visual discomfort, however, for dogs, the behaviour is the main criteria revealing the first signs of PRA's development. The progression of the disease is variable between individuals and breeds. For instance, Cardigan Welsh Corgi dogs become blind usually before one year of age with a fast progression of the disease when Irish and Gordon Setters, show clinical signs usually after 6 years of age (Chaudieu and Chahory 2013). The "early-onset PRA" implicates a disruption of the postnatal maturation of the retina (between 2 and 6 weeks of age) and/or a degeneration of cells that begins at the end or before the end of the development of the retina. The "late-onset PRA" develops later, after the complete maturation of the retina, the dog's retina being mature at 2 months old (Narfström and Petersen-Jones 2013).

Fundus presents lesions and pigmentary deposits

In all forms of PRA and RP the retina gets thinner and neuronal cells including photoreceptors progressively degenerate. The fundus of affected individuals shows pigment rearrangement with depigmented areas and pigment deposits (in peripheral region first, then towards the centre of the retina), a decrease of the vessel calibre and even their disappearance, a discoloured optic disc and consequently an atrophied optic nerve head. In dogs, the tapetal region appears granular at the beginning because of the degeneration of photoreceptors that evolves into a generalized hyperreflectivity of the tapetal area at the ultimate stage (Figs. 2, 3). Moreover, affected dogs present a reduction of the pupillary light response (Petersen-Jones 1998).

Table 1 Identified genes and mutations implicated in dog PRA

Gene name (chromosome)	Disease (transmission)	Mutation	Affected breed(s)	References
PDE6B (CFA3) β sub-unit of the phosphodiesterase	RCD 1 (AR) Rod Cone Dysplasia	G to A in exon 21 (TGG to stop codon TAG)	Irish setter	Suber et al. (1993)
	RCD 1a (AR) Rod Cone Dysplasia	8 bp insertion in exon 21	Sloughi	Dekomien et al. (2000)
RD3 (CFA7) Retinal Degeneration 3	RCD 2 (AR) Rod Cone Dysplasia	22 bp insertion in exon 4	Collie: smooth collie and rough collie	Kukekova et al. (2009)
PDE6A (CFA4) Phosphodiesterase 6 A, cGMP specific, rod, α sub-unit	RCD3 (AR) Rod Cone Dysplasia	1 bp deletion in exon 15	Cardigan Welsh Corgi	Petersen-Jones et al. (1999)
C2orf71 (CFA17) Chromosome 17 open reading frame, human C2orf71	RCD4 (AR) Rod Cone dysplasia	1 bp insertion in exon 1	Gordon Setter, Irish Setter	Downs et al. (2013)
SLC4A3 (CFA37) Solute Carrier Family 4, Anion Exchanger, Member 3	GR PRA 1 (AR) Golden Retriever Progressive retinal atrophy	1 bp insertion in exon 16	Golden Retriever	Downs et al. (2011)
TTC8 (CFA8) Tetratricopeptide repeat domain 8	GR PRA 2 (AR) Golden Retriever Progressive retinal atrophy	1 bp deletion in exon 8	Golden Retriever	Downs et al. (2014)
CCDC66 (CFA20) Coiled-coil domain containing 66	GPRA (AR) Generalized Progressive Retinal Atrophy	1 bp insertion in exon 6	Schapendoes	Dekomien et al. (2010)
PRCD (CFA9) Progressive Rod Cone Degeneration	PRCD (AR) Progressive rod-cone degeneration	G to A in exon 1 (TGC to TAC)	[a]	Zangerl et al. (2006)
RPGR (CFAX) Retinitis Pigmentosa GTPase regulator	XLPRA1 X linked Progressive Retinal Atrophy	5 bp deletion in exon 15	Siberian Husky Samoyede	Zhang et al. (2002)
	XLPRA2 X linked Progressive Retinal Atrophy	2 bp deletion in exon 15	Mongrel	
STK38L (CFA27) Serine/Threonine kinase 38 like	ERD (AR) Early Retinal Degeneration	SINE insertion in exon 4	Norwegian Elkhound	Goldstein et al. (2010)
RHO (CFA20) Rhodopsin	AD PRA Progressive Retinal Atrophy (AD)	C to G in exon 1	English Mastiff Bullmastiff	Kijas et al. (2002)
CNGB1 (CFA2) Cyclic Nucleotide Gated Channel beta 1	Progressive retinal atrophy (AR)	1 bp deletion + 6 bp insertion in exon 25	Papillon and Phalène	Ahonen et al. (2013)
SAG (CFA25) S-Antigen retina and pineal Gland (arrestin)	Progressive retinal atrophy (AR)	T to C in exon 18	Basenji	Goldstein et al. (2013)
CNGA1 (CFA13) Cyclic nucleotide gated channel alpha 1	Progressive retinal atrophy (AR)	4 bp deletion in exon 9	Shetland Sheepdog	Wiik et al. (2015)
FAM161A (CFA10) Family with sequence similarity 161, member A	Progressive retinal atrophy (AR)	SINE insertion of 132 pb in intron near exon 5	Tibetan spaniel, Tibetan Terrier	Downs and Mellersh (2014)
MERTK (CFA17) MER tyrosine kinase protooncogene	Progressive retinal atrophy (AR)	LINE-1 insertion in intron 1	Swedish Vallhund	Everson et al. (2017)

CFA canine chromosome, *AR* autosomal recessive, *AD* autosomal dominant, *del* deletion, *ins* insertion, *bp* base pair

[a]The mutation was highlighted in 18 different breeds (Zangerl et al. 2006), but over 50 breeds and 10 mixed breeds are tested by the Optigen company (http://www.optigen.com/opt9_test_prcd_pra.html; accessed 24 May 2018). Indeed, the mutation was recently found in other breeds and mixed breeds (Donner et al. 2018)

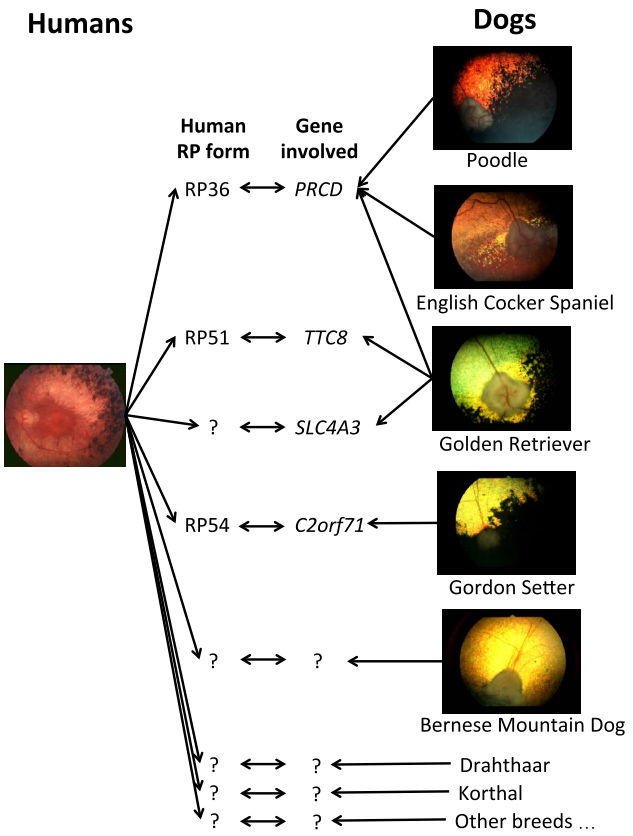

Fig. 2 Dog PRA as model for human RP. In dog, several dog breeds are affected by PRA and the implicated genes are the same than in human RP. Dog breeds for which the gene is not yet known thus represent good models to identify new candidate genes for human RP. Human eye fundus from C. Hamel. Dogs eye fundus from G. Chaudieu

The electroretinogram (ERG) shows a loss of rod functionality

The full field ERG is used for the exploration of the photoreceptors and the internal nuclear layer of the retina. It shows, in affected dogs, a hypovoltage of photoreceptors response more pronounced for rods resulting from their loss of function (Chaudieu et al. 2014). The advanced cases present a global extinction of the ERG waves in scotopic (rod response) and photopic conditions (cone response). In the late stage of the disease, the electroretinogram is not recordable. In most cases, the fundus is sufficient to make the diagnosis of PRA because the disease development is underway when owners notice loss of vision signs in their dogs. The ERG is essential in humans because it allows the detection of the degeneration before the earliest changes in the fundus and also allows the diagnosis in dogs. Indeed ERG shows abnormalities early in the development in the rods responses.

Mode of inheritance

In human, RP can be inherited as Mendelian or non-Mendelian traits. The most common mode of inheritance is autosomal recessive that represents 50–60% of total RP cases; then autosomal dominant, with 30–40%, and X-linked, with 5–15%. Non-Mendelian RP forms are less frequent and often belong to syndromic RP. Other inheritance modes combining several genes are also known, such as compound heterozygous mutations in the same gene or in different genes. For example a pseudo-dominant RP is caused by a combination of two heterozygous mutations in the *ROM1* and *PRPH2* genes (Kajiwara et al. 1994). In the Bardet Biedl syndrome, affected patients show a "triallelic digenic" inheritance mode (three alleles distributed over two genes) (Katsanis et al. 2001). In addition, a mutation in a mitochondrial gene has been reported to cause a syndromic RP associated with a hearing loss (Mansergh et al. 1999).

Canine PRA are mainly inherited as Mendelian traits: autosomal recessive, autosomal dominant or X-linked with a strong predominance of the autosomal recessive inheritance mode, due to the genetic history of dog breeds (inbreeding and use of popular sires increasing the probability to spread a mutation and to obtain homozygous dogs for the mutation) (Fig. 1). To date, numerous PRA forms have been described in the literature but the mode of inheritance is not always identified and is only presumed, unless exhaustive pedigree data or direct identification of the genes involved. For instance PRA is diagnosed in many breeds, but no pedigree information allowed yet to speculate the transmission mode, as for example PRA in the Wirehaired Pointing Dog (Drahthaar and Korthals) (Chaudieu and Chahory 2013), or in Bernese Mountain dogs (Chaudieu and Molon-Noblot 2004).

Dog PRA, human RP: similar metabolism, same genes involved

In 1978, the team of Dr. Aguirre first described a defect in the GMP metabolism implicated in a canine PRA, in the Irish setter breed called RCD1 (Rod Cone Dyslasia 1) (Aguirre 1978). Indeed, the functional and activated cGMP phophodiesterase (PDE) hydrolyses cGMP that is, at a low quantity, responsible for the closure of cation channels and consequently to the hyperpolarization of cell membranes. The GMP metabolism is essential in the phototransduction process, thus mutations of genes involved in this metabolism can lead to PRA. The 4 subunits of PDE were thus investigated in dog PRA (Figs. 2, 4), as well as in human RP. The β subunit of the phosphodiesterase (PDE6B) is mutated in an early onset PRA in Irish setter (Suber et al.

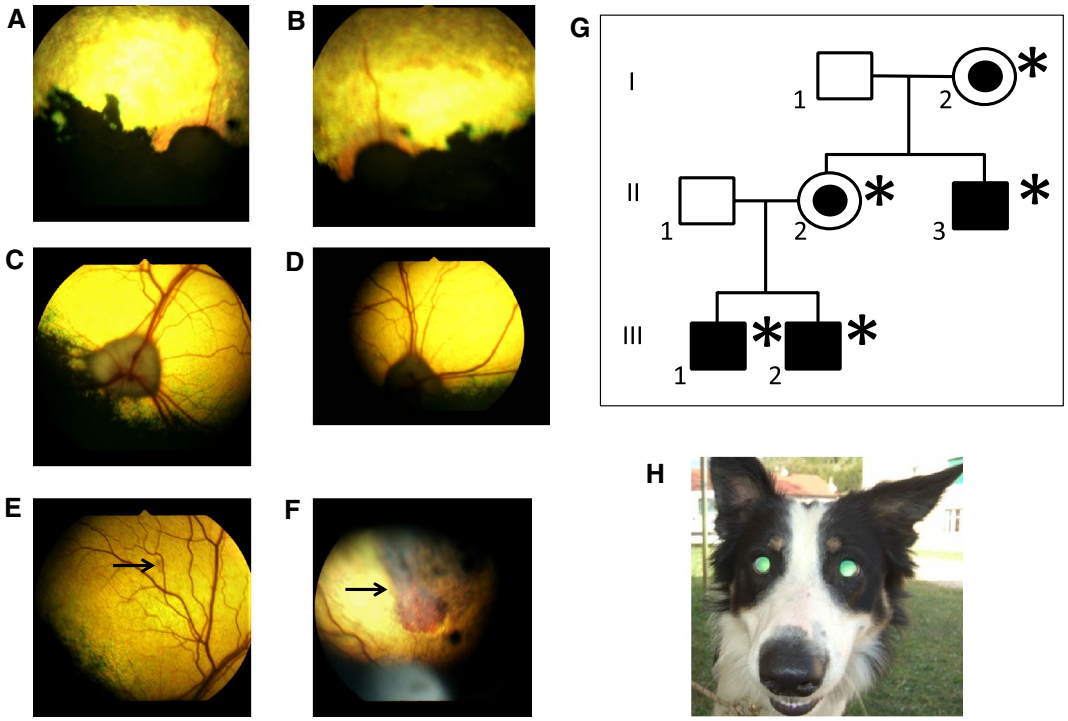

Fig. 3 Border collie PRA. Eye fundus of an affected male (**a, b**, dog II1 in the pedigree) and of her mother, obligate carrier (**c–f**, dog I2 in the pedigree) (photos from G. Chaudieu). **a, c** Left central eye fundus. **b, d** Right central eye fundus. **e** Left peripheral eye fundus. **f** Right peripheral eye fundus. **a, b** (Affected male): generalized retinal atrophy characterized by a hyperreflective tapetum, greyish pigmentation in the border of the tapetum as well as in non tapetal areas, no more arteries (only the dorsal vein is visible). **c, d** (Obligate carrier female): normal central eye fundus. A greyish pigmentation can be guessed in the periphery of the temporal tapetum for the left eye (**c**) and in the periphery of the nasal tapetum for the right eye (**d**). **e** In the left eye peripheral eye fundus, a small greyish pigmentation is observed in the tapetal area (arrow) as well as greyish pigmentation in the border of the tapetum as well as in non tapetal areas The vascularisation appears normal. **f** In the right eye peripheral eye fundus, a heterogeneous greyish pigmentation is observed in the tapetal area (arrow). The vascularisation appears normal. **g** Part of the Border collie pedigree, presenting the dog clinically described in **a–f**, and the genome of the dogs indicated by an asterisk has been sequenced. The females I2 and II2 are obligate carriers as they have affected sons. The 2 affected males III1 and III2 carry the affected X chromosome inherited from their II2 mother. **h** Picture of a 2-year old affected and blind Border collie (from E. Lafont)

1993) in a late onset PRA in Sloughi (Dekomien et al. 2000), as well as in human RP40 (McLaughlin et al. 1993; Bayés et al. 1995), one isolated autosomal recessive RP (Hmani-Aifa et al. 2009), and an autosomal dominant stationary night blindness 2 (CSNBAD2) (Gal et al. 1994). Concerning the α subunit (PDE6A), mutations were found in affected Cardigan Welsh corgi (Petersen-Jones et al. 1999), in human early onset night blindness (Huang et al. 1995) and in an autosomal recessive RP (Corton et al. 2010). No mutation was found in dogs in the other two subunits, PDE6γ and PDE6δ. In human, only few individuals affected with RP57 were found to have a mutation in the gamma subunit (Dvir et al. 2010).

Another key player was also investigated, the rhodopsin (RHO) (Figs. 2, 4). It is the G protein-coupled receptor that initiates the transduction cascade and allows the night vision. Mutations in the *RHO* gene are implicated in two different phenotypes (Gal et al. 1997; Cideciyan et al. 1998). To date, the Human Gene Mutation Database (HGMD: http://www.hgmd.cf.ac.uk/) references 4 mutations of this gene responsible for Congenital stationary Night blindness (CSNBAD1) and 209 mutations for retinitis pigmentosa 4 (RP4). In dog, Kijas et al. (2002) investigated the *RHO* gene in English Mastiff dog PRA because of clinical and ERG similarities with certain human *RHO*-linked RP. These similarities include a slow time course of recovery for rod cells after light exposure and localized thinning of the retina or a spread degeneration from a focal region. The specific PRA form segregates in English Mastiff and also in a related breed, Bullmastiff, evident by 12–18 months. A single nonsynonymous C to G transversion at nucleotide 11 of the *RHO* gene has been identified which changes Threonine into Arginine (T4R). However, the RHO expression or trafficking is not impaired by the mutation and retinal photoreceptors seem to develop normally (Kijas et al. 2003). To date, experiments to determine the function and the role of RHO in dog PRA have been performed in the "T4R RHO dog model" (Marsili et al. 2015; Iwabe et al. 2016).

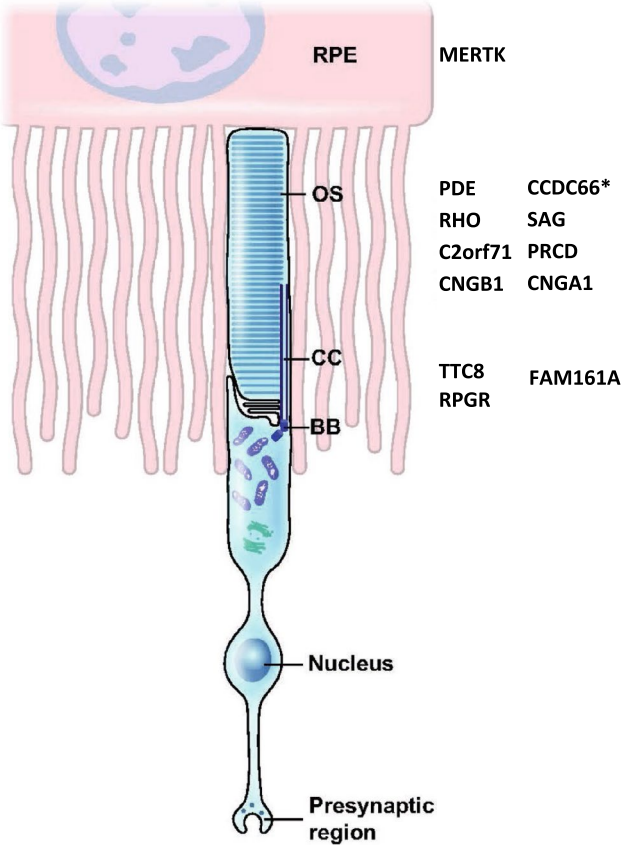

Fig. 4 Proteins for which mutation in the coding gene leads to canine PRA. Adapted from Veleri et al. (2015) (CC-BY license). Proteins are placed on the schematic of the retina according to their localization or function in photoreceptors and retinal pigment epithelium. Except for CCDC66, all the proteins have also been implicated in human RP. *RPE* retinal pigment epithelium, *OS* outer segment, *CC* connecting cilium, *BB* basal body of the photoreceptor (here a rod is represented)

A peculiar PRA form, really "late" compared to the other PRA, is described in the Gordon and Irish setter dogs, affected with RCD4 (Rod Cone Dysplasia 4), dogs being generally diagnosed around 10 years of age. The mutation leading to RCD4 is a single cytosine insertion in exon 1 of the *C2orf71*gene (Downs et al. 2013), which has a role in the morphogenesis of the photoreceptor outer segment (Corral-Serrano et al. 2018). A population study showed that RCD4 segregates in the Gordon Setter breed and in the Irish Setter breed with an allele frequency of 0.35 and 0.29, respectively. The *C2orf71* gene is also known to cause human RP, with, to date, 2 mutations found in two consanguineous families (Nishimura et al. 2010), and 3 mutations detected in three unrelated families (Collin et al. 2010). Further, 11 novel variants of *C2orf71* were detected in 286 unrelated individuals affected with progressive retinal degeneration. However, the authors concluded at a high level of polymorphism of this gene in the cases and controls population analyzed and mutations were not validated (Sergouniotis et al. 2011).

The two last genes discovered in late-onset PRA forms are *CNGB1* (Cyclic Nucleotide Gated Channel Beta 1) and *SAG* (Non-Stop S-antigen gene, also called Arrestin), both coding for proteins of the rod photoreceptors. The CNGB1 protein takes part in a cation channel to mediate the visual transduction cascade (Chen et al. 1993; Yau 1994; Körschen et al. 1995). The human *CNGB1* gene contains 33 exons and seven transcripts are expressed in the retina (Ardell et al. 2000). To date, 61 mutations in this gene have been reported to cause human RP in HGMD (Human Gene Mutation Database). In dogs, the two related breeds Papillon and Phalène are affected by a late onset PRA, also caused by a mutation leading to a frameshift and a premature stop codon in *CNGB1* (Ahonen et al. 2013). The *SAG* gene encodes a soluble rod outer-segment protein that binds light-activated phosphorylated rhodopsin to block phototransduction and target receptor to internalization (Wilden et al. 1986). Mutations in the *SAG* gene are implicated in human Oguchi disease 1 also called CSNBO1 (congenital stationary night blindness Oguchi type 1), which is characterized by a retarded course of dark adaptation of rod photoreceptors (Fuchs et al. 1995). This disease segregates as an autosomal recessive trait and 15 mutations have been reported in the *SAG* gene in human (HGMD). In dog, the Basenji breed exhibit a typical PRA diagnosed by 6–7 years of age and a mutation in the stop codon of the *SAG* gene leads to a predicted addition of 25 amino acids to the protein (Goldstein et al. 2013).

Interestingly, based on the identification of the *PRCD* gene in dogs, a human patient from Bangladesh affected with RP36 was homozygous for the same variant identified in the canine *PRCD* gene, and presented the same clinical signs as in dogs (Zangerl et al. 2006). Later, another mutation, a nonsense mutation, has been identified in the *PRCD* gene in 18 patients affected by RP, from 9 families of an Israeli Muslim Arab village (Nevet et al. 2010). The HGMD database is currently reporting 7 mutations in the human *PRCD* gene. Such findings confirm the founder effect of these mutations in human isolated populations, similarly to what is observed in isolated dog breeds. This gene first identified in canine PRA, then in human isolated populations affected with RP show the interest and ability of the dog model to highlight genes or pathways, not yet investigated in the human corresponding diseases.

For X-linked RP (XLRP), the most severe forms of RP with a prevalence of 1/25 000, the main gene is *RPGR* (RP GTPase regulator), with seven mutations first identified in a human X-linked RP, the retinitis pigmentosa 3 (RP3) (Meindl et al. 1996). Since then, 218 mutations (HGMD) had been identified in the human *RPGR* gene, but they are implicated in other human eye diseases like the X-linked cone dystrophy 1 or the X-linked recessive atrophic macular dystrophy. Further investigations of RPGR allowed to show its role in the photoreceptor cilium of the retina: RPGR

participates in the intraflagellar transport (Khanna et al. 2005), modulates the trafficking (Hosch et al. 2011) and may regulate the formation of the photoreceptor disc (Anand and Khanna 2012). To date, 70% of RP3 are explained (Vervoort et al. 2000) and the RP3 locus accounts for 60–90% of affected XLRP. Two other genes located on the X chromosome were also found to be mutated in human RP: *RP2* (Schwahn et al. 1998) and *OFD1* (Webb et al. 2012).

In dogs, two X-linked PRA have been described, also involving mutations in RPGR (Zeiss et al. 2000): one late-onset form, XLPRA1 (X-Linked Progressive Retinal Atrophy 1) in the Siberian Husky, and one early-onset, XLPRA2 (X-Linked Progressive Retinal Atrophy 2) in mongrel dogs. In the Siberian Husky a microdeletion was found in exon 15, and in mongrel dogs presenting ERG abnormalities by 5–6 weeks of age, a 2 bp deletion has been reported also in exon 15 (Zeiss et al. 2000). XLPRA1 is less severe that XLPRA2: for XLPRA1, the dog retina develops normally and remained functional until 6 months of age. After 6 months, ERG shows abnormalities and clinical signs appear in young adults (around 1,5 years). By mutation scanning, Zhang et al. (2002) showed that XLPRA1 also segregates in the Samoyed breed.

Some genes identified in dog breed specific PRA have not yet been implicated in human RP or retinopathies, thus constituting relevant candidates: the *SLC4A3* gene (solute carrier family 4, anion exchanger, member 3), *CCDC66* (coiled-coil domain containing 66) and *STK38L* (Serine/Threonine Kinase 38 like). Concerning *SLC4A3*, an insertion in exon 16 causing a premature stop codon, has been identified in a PRA late form in the Golden Retriever (age of onset 6–7 years) (Downs et al. 2011). This mutation is present in 56% of the PRA cases and 87% of obligate carriers in Golden Retrievers. Currently, the function of *SCL4A3* in PRA is still unknown and no mutation in this gene has been yet associated with spontaneous retinal degeneration in other species and humans. However, knockout mice for this gene present retinal degeneration with ERG, optic nerve and blood vessels anomalies (Alvarez et al. 2007). Concerning *CCDC66*, a 1 base deletion is responsible of Shapendoes PRA, which occurs between 2 and 5 years of age (Dekomien et al. 2010). A mouse model with a disrupted *CCDC66* gene showed a lack of retinal CCDC66 mRNA and protein expression leading to a progressive retinal degeneration (Gerding et al. 2011). Finally, concerning *STK38L*, it has been implicated in the early retinal degeneration disease in the Norwegian Elkhound dog breed and is inherited as an autosomal recessive trait; a SINE insertion in exon 4 of *STK38L* has been identified (Goldstein et al. 2010).

With similar clinical features and identical genes involved in RP and PRA, dogs thus constitute powerful models to discover new candidate genes for human RP for which causal mutations are to be found.

Border collie PRA as a model for human XL-RP

An XL-PRA segregating in the Border collie breed had previously been described (Chaudieu 2001; Chaudieu et al. 2014). This PRA is diagnosed by eye fundus, with an additional ERG if needed, at around 4 years of age. The clinical features have been extensively described (Chaudieu 2001; Chaudieu et al. 2014): a first loss of night vision is followed by a decrease of night and day vision that can lead to a complete blindness. Diffuse hyperreflectivity and migration of pigments in the tapetum area with a reduced vascularisation and a grey papilla characterised an advanced stage of the disease (Fig. 3). The prevalence of the disease is estimated to 8%, being around 2% for females and 16% for males (Chaudieu et al. 2014), fitting with the X linked mode of inheritance hypothesis. Since several years, over 1000 blood samples from affected and unaffected Border collies were collected through the Cani-DNA CRB. A pedigree consisting of over 300 dogs, including 89 affected dogs, 78 males and 11 females, and 120 unaffected dogs at an age over 5 years, allowed to confirm the recessive X linked mode of inheritance (Fig. 1) and to perform preliminary genetic analyses (Vilboux et al. 2008).

We recently genotyped a total of 178 related Border collies (including 36 affected dogs) on the Canine HD 170K SNP array (Illumina) or on the latest array containing 1 million SNPs (Affymetrix). Genetic linkage analysis showed that SNPs located on the X chromosome had the highest Lod score values (> 2). A closer look at the X chromosome genotypes showed that the region between 40 and 80 Mb is highly conserved in the 178 Border collies, independently of their clinical status (Unpublished data). More recently, large European and International consortiums, dedicated to canine genome sequences (DBVDC "Dog Biomedical Variant Database Consortium" and Dog 10 000 genomes) have been set up and allow us to use a whole genome sequencing (WGS) approach. While this approach is still expensive, it definitely allows to identify more causative or predisposing genes since it allows to point out mutations lying in potentially regulatory regions such as promotors and enhancers, or any potential regulatory non coding RNAs, intronic or splicing, mutations as well as structural variants. Indeed, more and more causal mutations are found in regulatory genetic regions in several diseases (Lin et al. 1999; Olsson et al. 2011; Plassais et al. 2016).

We thus selected five related Border collies from the pedigree and sequenced their genomes with the Illumina technology (Fig. 3). The I2 female presents mild symptoms and its expected genotype at the mutation can be homozygous or heterozygous since we know that few affected females with mild symptoms have unaffected fathers (with clinical

evaluation after 8 years old), indicating they are heterozygous. We compared the 5 Border collie genomes to 330 other dog genomes from 87 breeds (DBVDC) and identified a total of 78 single nucleotide variants (SNVs) on the X chromosome. These SNVs have been filtered (1) to present a different allele in the affected dogs compared to the dog reference genome, (2) to be heterozygous in the female II2 and (3) to be either homozygous or heterozygous in the female I2. None of these variants are located in coding regions and their involvement in the XL-PRA is still under investigation. In addition to SNVs, we searched for insertions, deletions, duplications, translocations and copy number variants by comparing the genome of the three affected dogs to the dog genomes from other breeds (DBVDC). The identified genetic alterations are now under investigation in additional affected and unaffected dogs to tentatively identify the causal mutation(s).

Our main hypothesis remains a recessive monogenic X-linked disease, affecting regulatory regions on the X chromosome, thus explaining the variability of the clinical features, age of onset and differential evolution of the lesions among affected females and between males and females. Indeed, the genetic status of affected females is never straightforward: independently of the lesions and their evolution, they can be homozygous or heterozygous, reflecting the X inactivation mechanism (Nanda et al. 2018). Finally, we do not exclude the co-existence of 2 clinically undistinguishable PRA forms, and several mutations segregating in the Border collie as it is the case for example, for the Golden retriever breed.

Conclusions

PRAs found in dogs serve as invaluable models for human RP, owing to the clinical, genetic and physiopathology similarities identified to date, leading to the availability of spontaneous models for numerous human retinal diseases. Indeed, in several instances, the genetic analyses of canine PRA led to the identification of the same genes in human families, as for the PRA-PRCD/RP36 form. This paper emphasizes the importance on the veterinary side of investigating and discovering novel PRA in dog breeds, and on the human side, of using these natural and spontaneous models of RP, in the hope of identifying novel human genes and mutation(s) in the corresponding RP.

Here, studying the Border collie PRA can hopefully lead to gene alteration(s) segregating in this breed and in patients affected with unknown forms of human RP. In human, only 3 genes involved in X-linked RP have yet been discovered (*RP2, OFD1* and *RPGR*), highlighting the complexity to identify the genetic cause of such X-linked diseases. We do hope that NGS approaches in nuclear canine families, with lots of affected cases and known obligate carriers, can by-pass the difficulties. Indeed, the use of dog breeds and the availability of hundreds of controls from many breeds for which a WGS is performed, constitute an exceptional tool for genetic research.

Characterizing "naturally" occurring animal models for human diseases is also a unique opportunity for the development of future treatments/therapeutic strategies in PRA/RP.

Importantly, the dog as a spontaneous homologous model of human RP is fully in respect of the 3R (Reduce, Refine, Replace) rule for managing animal models, *replacing* experimental rodent models in some instances. We also insist on the fact that such research also benefits dogs, by the development of genetic diagnosis and predictive tests, for a better management of the disease and of potential new treatments for dogs themselves.

Acknowledgements Authors dedicate this publication to Christian Hamel who tragically passed away during the writing of this paper. With great humility and sincerity, we dedicate this work to him. The authors are grateful to French referring veterinarians and to all dog owners and breeders who donated samples, pedigree data and follow-up of their dogs, especially the AFBC (Association Française du Border Collie), Mr. Cornuet, Mr. Fournier, Mr. Brimboeuf and Mrs Chartier, for transmitting the official eye clinical examination results as well as the ACT 43 (Association des Chiens de Troupeau de la Haute Loire) for participating to the funding of the whole genome sequencing of 3 dogs. We do thank breeders who welcome our research team in their kennels several years for sampling dogs, notably Mrs Malafayde, Mr. and Mrs Lalande, Mr and Mrs Laurent, Mr Garnier and Mrs Ladousse. We thank A.S. Lequarré and M.L Ramos-Pamplona, as coordinators for the European FP7 LUPA project, A. Boland and D. Zelenika for the genotyping performed at CNG, Evry, France. We do thank the members of DBVDC, dog whole genome sequencing consortium: Gus Aguirre, Catherine André, Danika Bannasch, Doreen Becker, Brian Davis, Cord Drögemüller, Kari Ekenstedt, Kiterie Faller, Oliver Forman, Steve Friedenberg, Eva Furrow, Urs Giger, Christophe Hitte, Marjo Hytönen, Tosso Leeb, Hannes Lohi, Cathryn Mellersh, Jim Mickelson, Leonardo Murgiano, Anita Oberbauer, Sheila Schmutz, Jeffrey Schoenebeck, Kim Summers, Frank van Steenbeek, Claire Wade. Blood and tissue samples from dogs were collected by a network of veterinarians through the Cani-DNA CRB (http://dog-genetics.genouest.org), which is part of the CRB-Anim infrastructure, ANR-11-INBS-0003. We thank Dr. Amandine Olivier for clinical data, Dr. Estèle Lafont for past molecular genetics experiments and the picture of the blind Border collie of Fig. 3, as well as Solenne Correard and Mélanie Rault for helpful discussions and advices. We also thank Antagene, Animal genetics laboratory, especially Anne Thomas and Guillaume Queney, for their involvement in the Border collie PRA project.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Acland GM, Aguirre GD, Ray J, Zhang Q, Aleman TS, Cideciyan AV, Pearce-Kelling SE, Anand V, Zeng Y, Maguire AM, Jacobson SG, Hauswirth WW, Bennett J (2001) Gene therapy restores vision in a canine model of childhood blindness. Nat Genet 28(1):92–95

Acland GM, Aguirre GD, Bennett J, Aleman TS, Cideciyan AV, Bennicelli J, Dejneka NS, Pearce-Kelling SE, Maguire AM, Palczewski K, Hauswirth WW, Jacobson SG (2005) Long-term restoration of rod and cone vision by single dose rAAV-mediated gene transfer to the retina in a canine model of childhood blindness. Mol Ther 12(6):1072–1082

Aguirre G (1978) Retinal degenerations in the dog. I. Rod dysplasia. Exp Eye Res 26(3):233–253

Aguirre GD, Acland GM (2006) Models, mutants, and man: searching for unique phenotypes and genes in the dog model of inherited retinal degeneration. In: Ostrander EA, Giger U, Lindblad-Toh K (eds) The dog and its genome. Cold Spring Harbor Laboratory Press, New York

Aguirre GK, Komáromy AM, Cideciyan AV, Brainard DH, Aleman TS, Roman AJ, Avants BB, Gee JC, Korczykowski M, Hauswirth WW, Acland GM, Aguirre GD, Jacobson SG (2007) Canine and human visual cortex intact and responsive despite early retinal blindness from RPE65 mutation. PLoS Med 4(6):e230

Ahonen SJ, Arumilli M, Lohi H (2013) A CNGB1 frameshift mutation in Papillon and Phalène dogs with progressive retinal atrophy. PLoS One 8(8):e72122. https://doi.org/10.1371/journal.pone.0072122

Alvarez BV, Gilmour GS, Mema SC, Martin BT, Shull GE, Casey JR, Sauvé Y (2007) Blindness caused by deficiency in AE3 chloride/bicarbonate exchanger. PLoS One 2(9):e839

Anand M, Khanna H (2012) Ciliary transition zone (TZ) proteins RPGR and CEP290: role in photoreceptor cilia and degenerative diseases. Expert Opin Ther Targ 16(6):541–551. https://doi.org/10.1517/14728222.2012.680956

Ardell MD, Bedsole DL, Schoborg RV, Pittler SJ (2000) Genomic organization of the human rod photoreceptor cGMP-gated cation channel beta-subunit gene. Gene 245(2):311–318

Bayés M, Giordano M, Balcells S, Grinberg D, Vilageliu L, Martínez I, Ayuso C, Benítez J, Ramos-Arroyo MA, Chivelet P et al (1995) Homozygous tandem duplication within the gene encoding the beta-subunit of rod phosphodiesterase as a cause for autosomal recessive retinitis pigmentosa. Hum Mutat 5(3):228–234

Beltran WA, Cideciyan AV, Lewin AS, Hauswirth WW, Jacobson SG, Aguirre GD (2014) Gene augmentation for X-linked retinitis pigmentosa caused by mutations in RPGR. Cold Spring Harb Perspect Med 5(2):a017392. https://doi.org/10.1101/cshperspect.a017392 **(review)**

Chaudieu G (2001) Etude de l'atrophie progressive de la rétine chez le Border Collie: Renseignements fournis par 213 examens pratiqués chez 161 chiens. Prat Méd Chir Anim Comp 36:55–73

Chaudieu G, Chahory S (2013) Affections oculaires héréditaires ou à prédisposition raciale chez le chien. 2nd ed. du point vétérinaire

Chaudieu G, Molon-Noblot S (2004) Early retinopathy in the Bernese Mountain Dog in France: preliminary observations. Vet Ophthalmol 7(3):175–184

Chaudieu G, Olivier A, Thomas A, Bunel M, Albaric O, Lafont E, Quignon P, André C (2014) Atrophie progressive de la rétine du Border Collie: étude rétrospective (1996–2012). Revue vétérinaire Clinique 49:93–101

Chen TY, Peng YW, Dhallan RS, Ahamed B, Reed RR, Yau KW (1993) A new subunit of the cyclic nucleotide-gated cation channel in retinal rods. Nature 362(6422):764–767

Cideciyan AV, Hood DC, Huang Y, Banin E, Li ZY, Stone EM, Milam AH, Jacobson SG (1998) Disease sequence from mutant rhodopsin allele to rod and cone photoreceptor degeneration in man. Proc Natl Acad Sci USA 95(12):7103–7108

Collin RW, Safieh C, Littink KW, Shalev SA, Garzozi HJ, Rizel L, Abbasi AH, Cremers FP, den Hollander AI, Klevering BJ, Ben-Yosef T (2010) Mutations in C2ORF71 cause autosomal-recessive retinitis pigmentosa. Am J Hum Genet 86(5):783–788. https://doi.org/10.1016/j.ajhg.2010.03.016

Corral-Serrano JC, Messchaert M, Dona M, Peters TA, Kamminga LM, van Wijk E, Collin RWJ (2018) C2orf71a/pcare1 is important for photoreceptor outer segment morphogenesis and visual function in zebrafish. Sci Rep 8(1):9675. https://doi.org/10.1038/s41598-018-27928-7

Corton M, Blanco MJ, Torres M, Sanchez-Salorio M, Carracedo A, Brion M (2010) Identification of a novel mutation in the human PDE6A gene in autosomal recessive retinitis pigmentosa: homology with the nmf28/nmf28 mice model. Clin Genet 78(5):495–498. https://doi.org/10.1111/j.1399-0004.2010.01487.x

Daiger SP, Sullivan LS, Bowne SJ (2013) Genes and mutations causing retinitis pigmentosa. Clin Genet 84(2):132–141. https://doi.org/10.1111/cge.12203

Dekomien G, Runte M, Gödde R, Epplen JT (2000) Generalized progressive retinal atrophy of Sloughi dogs is due to an 8-bp insertion in exon 21 of the PDE6B gene. Cytogenet Cell Genet 90(3–4):261–267

Dekomien G, Vollrath C, Petrasch-Parwez E, Boevé MH, Akkad DA, Gerding WM, Epplen JT (2010) Progressive retinal atrophy in Schapendoes dogs: mutation of the newly identified CCDC66 gene. Neurogenetics 11(2):163–174. https://doi.org/10.1007/s10048-009-0223-z

Donner J, Anderson H, Davison S, Hughes AM, Bouirmane J, Lindqvist J, Lytle KM, Ganesan B, Ottka C, Ruotanen P, Kaukonen M, Forman OP, Fretwell N, Cole CA, Lohi H (2018) Frequency and distribution of 152 genetic disease variants in over 100,000 mixed breed and purebred dogs. PLoS Genet 14(4):e1007361. https://doi.org/10.1371/journal.pgen.1007361

Downs LM, Mellersh CS (2014) An Intronic SINE insertion in FAM161A that causes exon-skipping is associated with progressive retinal atrophy in Tibetan Spaniels and Tibetan Terriers. PLoS One 9(4):e93990. https://doi.org/10.1371/journal.pone.0093990

Downs LM, Wallin-Håkansson B, Boursnell M, Marklund S, Hedhammar Å, Truvé K, Hübinette L, Lindblad-Toh K, Bergström T, Mellersh CS (2011) A frameshift mutation in golden retriever dogs with progressive retinal atrophy endorses SLC4A3 as a candidate gene for human retinal degenerations. PLoS One 6(6):e21452. https://doi.org/10.1371/journal.pone.0021452

Downs LM, Bell JS, Freeman J, Hartley C, Hayward LJ, Mellersh CS (2013) Late-onset progressive retinal atrophy in the Gordon and Irish Setter breeds is associated with a frameshift mutation in C2orf71. Anim Genet 44(2):169–177. https://doi.org/10.1111/j.1365-2052.2012.02379.x

Downs LM, Wallin-Håkansson B, Bergström T, Mellersh CS (2014) A novel mutation in TTC8 is associated with progressive retinal atrophy in the golden retriever. Canine Genet Epidemiol 1:4. https://doi.org/10.1186/2052-6687-1-4

Dvir L, Srour G, Abu-Ras R, Miller B, Shalev SA, Ben-Yosef T (2010) Autosomal-recessive early-onset retinitis pigmentosa caused by a mutation in PDE6G, the gene encoding the gamma subunit of rod cGMP phosphodiesterase. Am J Hum Genet 87(2):258–264. https://doi.org/10.1016/j.ajhg.2010.06.016

Everson R, Pettitt L, Forman OP, Dower-Tylee O, McLaughlin B, Ahonen S, Kaukonen M, Komáromy AM, Lohi H, Mellersh CS, Sansom J, Ricketts SL (2017) An intronic LINE-1 insertion in MERTK is strongly associated with retinopathy in Swedish Vallhund dogs. PLoS One 12(8):e0183021

Fuchs S, Nakazawa M, Maw M, Tamai M, Oguchi Y, Gal A (1995) A homozygous 1-base pair deletion in the arrestin gene is a frequent cause of Oguchi disease in Japanese. Nat Genet 10(3):360–362

Gal A, Orth U, Baehr W, Schwinger E, Rosenberg T (1994) Heterozygous missense mutation in the rod cGMP phosphodiesterase beta-subunit gene in autosomal dominant stationary night blindness. Nat Genet 7(1):64–68

Gal A, Apfelstedt-Sylla E, Janecke AR, Zrenner E (1997) Rhodopsin mutations in inherited retinal dystrophies and dysfunctions. Prog Retinal Eye Res 16(1):51–79

Galibert F, Quignon P, Hitte C, André C (2011) Toward understanding dog evolutionary and domestication history. C R Biol 334(3):190–196. https://doi.org/10.1016/j.crvi.2010.12.011

Gerding WM, Schreiber S, Schulte-Middelmann T, de Castro Marques A, Atorf J, Akkad DA, Dekomien G, Kremers J, Dermietzel R, Gal A, Rülicke T, Ibrahim S, Epplen JT, Petrasch-Parwez E (2011) Ccdc66 null mutation causes retinal degeneration and dysfunction. Hum Mol Genet 20(18):3620–3631. https://doi.org/10.1093/hmg/ddr282

Goldstein O, Zangerl B, Pearce-Kelling S, Sidjanin DJ, Kijas JW, Felix J, Acland GM, Aguirre GD (2006) Linkage disequilibrium mapping in domestic dog breeds narrows the progressive rod-cone degeneration interval and identifies ancestral disease-transmitting chromosome. Genomics 88(5):541–550

Goldstein O, Kukekova AV, Aguirre GD, Acland GM (2010) Exonic SINE insertion in STK38L causes canine early retinal degeneration (erd). Genomics 96(6):362–368. https://doi.org/10.1016/j.ygeno.2010.09.003

Goldstein O, Jordan JA, Aguirre GD, Acland GM (2013) A non-stop S-antigen gene mutation is associated with late onset hereditary retinal degeneration in dogs. Mol Vis 19:1871–1884

Grall A, Guaguère E, Planchais S, Grond S, Bourrat E, Hausser I, Hitte C, Le Gallo M, Derbois C, Kim GJ, Lagoutte L, Degorce-Rubiales F, Radner FP, Thomas A, Küry S, Bensignor E, Fontaine J, Pin D, Zimmermann R, Zechner R, Lathrop M, Galibert F, André C, Fischer J (2012) PNPLA1 mutations cause autosomal recessive congenital ichthyosis in golden retriever dogs and humans. Nat Genet 44(2):140–147. https://doi.org/10.1038/ng.1056

Hamel C (2006) Retinitis pigmentosa. Orphanet J Rare Dis 1:40 **(review)**

Hmani-Aifa M, Benzina Z, Zulfiqar F, Dhouib H, Shahzadi A, Ghorbel A, Rebaï A, Söderkvist P, Riazuddin S, Kimberling WJ, Ayadi H (2009) Identification of two new mutations in the GPR98 and the PDE6B genes segregating in a Tunisian family. Eur J Hum Genet 17(4):474–482. https://doi.org/10.1038/ejhg.2008.167

Hosch J, Lorenz B, Stieger K (2011) RPGR: role in the photoreceptor cilium, human retinal disease, and gene therapy. Ophthalm Genet 32(1):1–11. https://doi.org/10.3109/13816810.2010.535889

Huang SH, Pittler SJ, Huang X, Oliveira L, Berson EL, Dryja TP (1995) Autosomal recessive retinitis pigmentosa caused by mutations in the alpha subunit of rod cGMP phosphodiesterase. Nat Genet 11(4):468–471

Iwabe S, Ying GS, Aguirre GD, Beltran WA (2016) Assessment of visual function and retinal structure following acute light exposure in the light sensitive T4R rhodopsin mutant dog. Exp Eye Res 146:341–353. https://doi.org/10.1016/j.exer.2016.04.006

Kajiwara K, Berson EL, Dryja TP (1994) Digenic retinitis pigmentosa due to mutations at the unlinked peripherin/RDS and ROM1 loci. Science 264(5165):1604–1608

Katsanis N, Ansley SJ, Badano JL, Eichers ER, Lewis RA, Hoskins BE, Scambler PJ, Davidson WS, Beales PL, Lupski JR (2001) Triallelic inheritance in Bardet-Biedl syndrome, a Mendelian recessive disorder. Science 293(5538):2256–2259

Khanna H, Hurd TW, Lillo C, Shu X, Parapuram SK, He S, Akimoto M, Wright AF, Margolis B, Williams DS, Swaroop A (2005) RPGR-ORF15, which is mutated in retinitis pigmentosa, associates with SMC1, SMC3, and microtubule transport proteins. J Biol Chem 280(39):33580–33587

Kijas JW, Cideciyan AV, Aleman TS, Pianta MJ, Pearce-Kelling SE, Miller BJ, Jacobson SG, Aguirre GD, Acland GM (2002) Naturally occurring rhodopsin mutation in the dog causes retinal dysfunction and degeneration mimicking human dominant retinitis pigmentosa. Proc Natl Acad Sci USA 99(9):6328–6333

Kijas JW, Miller BJ, Pearce-Kelling SE, Aguirre GD, Acland GM (2003) Canine models of ocular disease: outcross breedings define a dominant disorder present in the English mastiff and bull mastiff dog breeds. J Hered 94(1):27–30

Körschen HG, Illing M, Seifert R, Sesti F, Williams A, Gotzes S, Colville C, Müller F, Dosé A, Godde M et al (1995) A 240 kDa protein represents the complete beta subunit of the cyclic nucleotide-gated channel from rod photoreceptor. Neuron 15(3):627–636

Kukekova AV, Goldstein O, Johnson JL, Richardson MA, Pearce-Kelling SE, Swaroop A, Friedman JS, Aguirre GD, Acland GM (2009) Canine RD3 mutation establishes rod-cone dysplasia type 2 (rcd2) as ortholog of human and murine rd3. Mamm Genome 20(2):109–123. https://doi.org/10.1007/s00335-008-9163-4

Lin L, Faraco J, Li R, Kadotani H, Rogers W, Lin X, Qiu X, de Jong PJ, Nishino S, Mignot E (1999) The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. Cell 98(3):365–376

Lorant J, Larcher T, Jaulin N, Hedan B, Lardenois A, Leroux I, Dubreil L, Ledevin M, Goubin H, Moullec S, Deschamps JY, Thorin C, André C, Adjali O, Rouger K (2018) Vascular delivery of allogeneic mustem cells in dystrophic dogs requires only short-term immunosuppression to avoid host immunity and generate clinical/tissue benefits. Cell Transpl 27(7):1096–1110

Magnusson H (1911) Uber retinites pigmentosa und konsanguinitat beim hunde (On retinitis pigmentosa and consanguinity in dogs). Arch Vergi Ophthalmol 2:147

Mansergh FC, Millington-Ward S, Kennan A, Kiang AS, Humphries M, Farrar GJ, Humphries P, Kenna PF (1999) Retinitis pigmentosa and progressive sensorineural hearing loss caused by a C12258A mutation in the mitochondrial MTTS2 gene. Am J Hum Genet 64(4):971–985

Marsili S, Genini S, Sudharsan R, Gingrich J, Aguirre GD, Beltran WA (2015) Exclusion of the unfolded protein response in light-induced retinal degeneration in the canine T4R RHO model of autosomal dominant retinitis pigmentosa. PLoS One 10(2):e0115723. https://doi.org/10.1371/journal.pone.0115723

Martin-Merida I, Aguilera-Garcia D, Fernandez-San Jose P, Blanco-Kelly F, Zurita O, Almoguera B, Garcia-Sandoval B, Avila-Fernandez A, Arteche A, Minguez P, Carballo M, Corton M, Ayuso C (2018) Toward the mutational landscape of autosomal dominant retinitis pigmentosa: a comprehensive analysis of 258 Spanish families. Invest Ophthalmol Vis Sci 59(6):2345–2354

McLaughlin ME, Sandberg MA, Berson EL, Dryja TP (1993) Recessive mutations in the gene encoding the beta-subunit of rod phosphodiesterase in patients with retinitis pigmentosa. Nat Genet 4(2):130–134

Meindl A, Dry K, Herrmann K, Manson F, Ciccodicola A, Edgar A, Carvalho MR, Achatz H, Hellebrand H, Lennon A, Migliaccio C, Porter K, Zrenner E, Bird A, Jay M, Lorenz B, Wittwer B, D'Urso M, Meitinger T, Wright A (1996) A gene (RPGR) with homology to the RCC1 guanine nucleotide exchange factor is mutated in X-linked retinitis pigmentosa (RP3). Nat Genet 13(1):35–42

Nanda A, Salvetti AP, Clouston P, Downes SM, MacLaren RE (2018) Exploring the variable phenotypes of RPGR carrier females in assessing their potential for retinal gene therapy. Genes (Basel) 9(12):E643. https://doi.org/10.3390/genes9120643

Narfström K, Petersen-Jones SM (2013) Diseases of the Canine Ocular Fundus. In: Gelatt KN, Gilger BC, Kern TJ (eds) Veterinary ophtalmology, 5th edn. Wiley, Iowa, pp 1303–1393

Nevet MJ, Shalev SA, Zlotogora J, Mazzawi N, Ben-Yosef T (2010) Identification of a prevalent founder mutation in an Israeli Muslim Arab village confirms the role of PRCD in the aetiology of retinitis pigmentosa in humans. J Med Genet 47(8):533–537. https://doi.org/10.1136/jmg.2009.073619

Nishimura DY, Baye LM, Perveen R, Searby CC, Avila-Fernandez A, Pereiro I, Ayuso C, Valverde D, Bishop PN, Manson FD, Urquhart J, Stone EM, Slusarski DC, Black GC, Sheffield VC (2010) Discovery and functional analysis of a retinitis pigmentosa gene, C2ORF71. Am J Hum Genet 86(5):686–695. https://doi.org/10.1016/j.ajhg.2010.03.005

Olsson M, Meadows JR, Truvé K, RosengrenPielberg G, Puppo F, Mauceli E, Quilez J, Tonomura N, Zanna G, Docampo MJ, Bassols A, Avery AC, Karlsson EK, Thomas A, Kastner DL, Bongcam-Rudloff E, Webster MT, Sanchez A, Hedhammar A, Remmers EF, Andersson L, Ferrer L, Tintle L, Lindblad-Toh K (2011) A novel unstable duplication upstream of HAS2 predisposes to a breed-defining skin phenotype and a periodic fever syndrome in Chinese Shar-Pei dogs. PLoS Genet 7(3):e1001332

Pagon RA (1988) Retinitis pigmentosa. Surv Ophthalmol 33(3):137–177 **(review)**

Pary HB (1953) Degenerations of the dog retina. III. Retinopathy secondary to glaucoma. Br J Ophthalmol 37(11):670–679

Patterson DF (2000) Companion animal medicine in the age of medical genetics. J Vet Intern Med 14(1):1–9

Petersen-Jones SM (1998) Animal models of human retinal dystrophies. Eye (Lond) 12(Pt 3b):566–570 **(review)**

Petersen-Jones S (2005) Advances in the molecular understanding of canine retinal diseases. J Small Anim Pract 46(8):371–380 **(review)**

Petersen-Jones SM, Komáromy AM (2015) Dog models for blinding inherited retinal dystrophies. Hum Gene Ther Clin Dev 26(1):15–26. https://doi.org/10.1089/humc.2014.155 **(review)**

Petersen-Jones SM, Entz DD, Sargan DR (1999) cGMP phosphodiesterase-alpha mutation causes progressive retinal atrophy in the Cardigan Welsh corgi dog. Invest Ophthalmol Vis Sci 40(8):1637–1644

Pichard V, Provost N, Mendes-Madeira A, Libeau L, Hulin P, Tshilenge KT, Biget M, Ameline B, Deschamps JY, Weber M, Le Meur G, Colle MA, Moullier P, Rolling F (2016) AAV-mediated gene therapy halts retinal degeneration in PDE6β-deficient dogs. Mol Ther 24(5):867–876. https://doi.org/10.1038/mt.2016.37 **(Epub 2016 Feb 9)**

Plassais J, Guaguère E, Lagoutte L, Guillory AS, de Citres CD, Degorce-Rubiales F, Delverdier M, Vaysse A, Quignon P, Bleuart C, Hitte C, Fautrel A, Kaerle C, Bellaud P, Bensignor E, Queney G, Bourrat E, Thomas A, André C (2014) A spontaneous KRT16 mutation in a dog breed: a model for human focal non-epidermolytic palmoplantar keratoderma (FNEPPK). J Invest Dermatol 135(4):1187–1190

Plassais J, Lagoutte L, Correard S, Paradis M, Guaguère E, Hédan B, Pommier A, Botherel N, Cadiergues MC, Pilorge P, Silversides D, Bizot M, Samuels M, Arnan C, Johnson R, Hitte C, Salbert G, Méreau A, Quignon P, Derrien T, André C (2016) A point mutation in a lincRNA upstream of GDNF is associated to a canine insensitivity to pain: a spontaneous model for human sensory neuropathies. PLoS Genet 12(12):e1006482. https://doi.org/10.1371/journal.pgen.1006482

Rouger K, Larcher T, Dubreil L, Deschamps JY, Le Guiner C, Jouvion G, Delorme B, Lieubeau B, Carlus M, Fornasari B, Theret M, Orlando P, Ledevin M, Zuber C, Leroux I, Deleau S, Guigand L, Testault I, Le Rumeur E, Fiszman M, Chérel Y (2011) Systemic delivery of allogenic muscle stem cells induces long-term muscle repair and clinical efficacy in duchenne muscular dystrophy dogs. Am J Pathol 179(5):2501–2518. https://doi.org/10.1016/j.ajpath.2011.07.022

Schwahn U, Lenzner S, Dong J, Feil S, Hinzmann B, van Duijnhoven G, Kirschner R, Hemberger M, Bergen AA, Rosenberg T, Pinckers AJ, Fundele R, Rosenthal A, Cremers FP, Ropers HH, Berger W (1998) Positional cloning of the gene for X-linked retinitis pigmentosa 2. Nat Genet 19(4):327–332

Sergouniotis PI, Li Z, Mackay DS, Wright GA, Borman AD, Devery SR, Moore AT, Webster AR (2011) A survey of DNA variation of C2ORF71 in probands with progressive autosomal recessive retinal degeneration and controls. Invest Ophthalmol Vis Sci 52(3):1880–1886. https://doi.org/10.1167/iovs.10-6043

Suber ML, Pittler SJ, Qin N, Wright GC, Holcombe V, Lee RH, Craft CM, Lolley RN, Baehr W, Hurwitz RL (1993) Irish setter dogs affected with rod/cone dysplasia contain a nonsense mutation in the rod cGMP phosphodiesterase beta-subunit gene. Proc Natl Acad Sci USA 90(9):3968–3972

Veleri S, Lazar CH, Chang B, Sieving PA, Banin E, Swaroop A (2015) Biology and therapy of inherited retinal degenerative disease: insights from mouse models. Dis Model Mech 8(2):109–129. https://doi.org/10.1242/dmm.017913

Verbakel SK, van Huet RAC, Boon CJF, den Hollander AI, Collin RWJ, Klaver CCW, Hoyng CB, Roepman R, Klevering BJ (2018) Non-syndromic retinitis pigmentosa. Prog Retin Eye Res 66:157–186. https://doi.org/10.1016/j.preteyeres.2018.03.005

Vervoort R, Lennon A, Bird AC, Tulloch B, Axton R, Miano MG, Meindl A, Meitinger T, Ciccodicola A, Wright AF (2000) Mutational hot spot within a new RPGR exon in X-linked retinitis pigmentosa. Nat Genet 25(4):462–466

Vilboux T, Chaudieu G, Jeannin P, Delattre D, Hedan B, Bourgain C, Queney G, Galibert F, Thomas A, André C (2008) Progressive retinal atrophy in the Border Collie: a new XLPRA. BMC Vet Res 4:10. https://doi.org/10.1186/1746-6148-4-10

Webb TR, Parfitt DA, Gardner JC, Martinez A, Bevilacqua D, Davidson AE, Zito I, Thiselton DL, Ressa JH, Apergi M, Schwarz N, Kanuga N, Michaelides M, Cheetham ME, Gorin MB, Hardcastle AJ (2012) Deep intronic mutation in OFD1, identified by targeted genomic next-generation sequencing, causes a severe form of X-linked retinitis pigmentosa (RP23). Hum Mol Genet 21(16):3647–3654. https://doi.org/10.1093/hmg/dds194

Wiik AC, Ropstad EO, Ekesten B, Karlstam L, Wade CM, Lingaas F (2015) Progressive retinal atrophy in Shetland sheep dog is associated with a mutation in the CNGA1gene. Anim Genet 46(5):515–521. https://doi.org/10.1111/age.12323

Wilden U, Hall SW, Kühn H (1986) Phosphodiesterase activation by photoexcited rhodopsin is quenched when rhodopsin is phosphorylated and binds the intrinsic 48-kDa protein of rod outer segments. Proc Natl Acad Sci USA 83(5):1174–1178

Yau KW (1994) Cyclic nucleotide-gated channels: an expanding new family of ion channels. Proc Natl Acad Sci USA 91(9):3481–3483 **(review)**

Zangerl B, Goldstein O, Philp AR, Lindauer SJ, Pearce-Kelling SE, Mullins RF, Graphodatsky AS, Ripoll D, Felix JS, Stone EM, Acland GM, Aguirre GD (2006) Identical mutation in a novel retinal gene causes progressive rod-cone degeneration in dogs and retinitis pigmentosa in humans. Genomics 88(5):551–563

Zeiss CJ, Ray K, Acland GM, Aguirre GD (2000) Mapping of X-linked progressive retinal atrophy (XLPRA), the canine homolog of retinitis pigmentosa 3 (RP3). Hum Mol Genet 9(4):531–537

Zhang Q, Acland GM, Wu WX, Johnson JL, Pearce-Kelling S, Tulloch B, Vervoort R, Wright AF, Aguirre GD (2002) Different RPGR exon ORF15 mutations in Canids provide insights into photoreceptor cell degeneration. Hum Mol Genet 11(9):993–1003