Swedish University of Agricultural Sciences
Faculty of Veterinary Medicine and Animal Science

Differences of Progressive Retinal Atrophy in dogs

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Skillnader i progressiv retinal atrofi hos hund

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Contents

Sammanfattning 2
Abstract 2
Introduction 2
Background 3
Basic genetics 4
Inherited retinal degeneration 4
Retinitis pigmentosa and Progressive retinal atrophy 5
Progressive retinal dysplasia 7
1: CNGB3 Canine cone degeneration 7
2: CORD1 Cone-Rod Dystrophy (cord) 8
3: NPHP4 Cone-Rod Dystrophy, type 2 8
4: PDC Photoreceptor dysplasia 9
5: PRA – autosomal dominant 9
6: PRA cone-rod dystrophy, type 1 9
7: PRA cone-rod dystrophy, type 2 9
8: PRA cone-rod dystrophy, type 3 9
9: PRA X-linked 10
10: Retinal degeneration, early 10
11: Retinal degeneration, type 2 10
12: Retinal pigment epithelial dystrophy 11
13: Retinopathy, multifocal 11
14: Rod-cone degeneration, progressive 11
15: Rod-cone dysplasia 11
Discussion 11
References 13

Sammanfattning

En grupp av sjukdomar som drabbar hundars syn är progressiv retina atrophy (PRA), en sjukdom som innebär att fotoreceptorerna i ögats retina antingen inte utvecklas normalt eller genomgår en degeneration och därigenom orsakar synreduktion och blindhet. Sjukdomen drabbar många olika raser och är ärftlig. Det har visat sig att det är helt olika gener som drabbats av mutationer i de olika raserna så trots att sjukdomen har relativt likvärdiga kliniska symptom så kan den bakomliggande orsaken vara olika. Hos människor finns det en stor grupp sjukdomar som går under namnet Retinitis pigmentosa (RP) och är den homologa motsvarigheten till hundens PRA. Detta är en studie av sjukdomens förlopp hos både hund och människa samt en sammanställning av de mutationer som ligger till grund för sjukdomarna hos hund.

Abstract

A group of diseases that affect the dog's sight is progressive retinal atrophy (PRA) a disease that means that the photoreceptors in the retina of the eye either not develop normally or undergo degeneration and thereby causes vision loss and blindness. The disease affects many different breeds and is inherited. What have been shown is that it is different genes that had become mutated in the different breeds, this conclude that despite similar clinical symptoms, the underlying reason could be different. Also the genes that are mutated in dogs and give rise to diseases also exists in humans. In humans there is a big group of diseases that goes under the name Retinitis pigmentosa (RP) and it is equivalent to PRA. This is a review of the progression of the disease in both humans and dogs and also a comparison of the mutations that causes the diseases in dogs.

Introduction

Dogs are a part of many people's life. We make bounds to them and care for them deeply, they help society in many ways, all the way from police dogs to company to elderly. We control their reproduction and inherited traits passed down can cause them suffering. As our close companions their well being are an important thing, both because of our empathy and love for them and also for animal welfare aspects. At OMIA (Online Mendelian Inheritance in Animal) 503 known genes that causes disease in dogs are listed and described and in 233 of them there are potential models for human disease (OMIA, 2010). Dogs have therefore several features that make them both interesting in the search of animal models to many human diseases and also important from a social view.

Problems with sight cause lots of disadvantages and suffering to affected individuals. Many dog breeds suffer from an inherited group of retinal diseases that causes the retina to degenerate. The phenotypic symptom is a progressive visual impairment but onset, inheritance and clinical symptoms vary. It is shown that the mutation that cause these diseases vary between breeds, some breeds have one type and other, and interestingly do all the forms of known mutations also exist in humans. Therefore studies on dogs are valuable for human health, not only for the wellbeing of a companion.

Background

Since the dog, or actually the ancestral wolf, joined humans and became domesticated, an artificial selection of specific traits have been made (Wilcox & Walkowicz, 1993). First archaeological findings of dogs (wolves) together with humans are dated 300.000 years BP (before present) (Galibert et al., 2011). These signs of humans and wolves living together are not evidence live that wolves hd been domesticated, only that they started to live close together. The first findings that could proof wolves have become domesticated and started to become more of a dog instead of a wolf is form fossil dated 31.700 years BP, where the skull of a wolf buried together with a human is different shaped than a wild wolf skull (Germonpre´ et al. 2009). Theories about why the wolf become domesticated differ but the most scientists believe that wolves in search of food kept close to humans and in situations where one of these close-living wolf was killed there was a chance that it's pups were kept alive and tamed. Younger archaeological findings show that the dogs/wolves living among humans differ in size from wild wolves, giving a theory that the breeding started to be under some form of control. (Galibert, et al. 2011). Even though humans interfered in the mating between them, it is not until 6-7000 years BP there actually is a distinctive breed, the Saluki. In ancient Egypt, 3000 years BP the dog had been divided more and more into separate breeds or groups' which had different roles; guarding, hunting and just company. The big amount of various breeds that we have today began to form as late as the last centuries. To date there are about 400 specific breeds acknowledged by the big breeding societies.

By the construction of the many breeds we have today, often just a few dogs have been used as founders and it has caused a bottleneck effect and decreased the allelic variation within the breed and concentrate homozygous alleles. When looking at the dog genome the linkage disequilibrium within breeds it last several megabasepairs but on other hand between breeds it only extend of at a length of kilobasepairs (Lindblad-Toh, 2005). This are signs for bottlenecks in the history of dogs, also a high frequency of inbreeding during the building of new breeds has made random mutations spread throughout the population (Sutter et al., 2004). This has affected the genome in the way that inherited diseases appear more frequent.

To date there are 160 identified genes for inherited retinal diseases in humans and homologues in other species could be used as valuable animal models (Retnet, 2010). Retinopathies are a group of inherited diseases among several species in which the retina in the eye becomes more and more degenerative. Retinal diseases are common also among humans and approximately one in 2000 individuals are affected of some type of retinopathy. (Sohocki et al., 2000). The inherited forms of retinopathies could be caused by several different mutations and depending on which gene that is affected and on which chromosome the gene is on, both the phenotype and the inheritance vary. To date there are 160 identified genes for inherited retinal diseases in humans and homologues in other species could be used as valuable animal models (Retnet, 2010).

The eye is exposed to a diverse group of inherited diseases causing retinal degeneration, giving progressive vision impairment and eventually blindness (Phelan & Bok, 2000: Mellersh et al., 2006). The cluster name for bilateral, progressively degeneration of the retina, leading to blindness or sever vision losses is Progressive Retinal Atrophy (PRA) (Ofri & Narfström, 2006). The human homologue for these retinal dysfunction diseases is Retinitis Pigmentosa (RP) (Phelan & Bok, 2000). Associated diseases are Leber congenital amaurosis, Stargardt disease, fundus flavimaculatus, macular degeneration, cone dystrophy and refsum disease, which all include degenerating of retinal cells. Of these mentioned diseases the majority also exist in dogs. Retinopathies are a broad group of diseases were the cause and

progression vary. Several different diseases, which all include degeneration of cones and rods in the retina are grouped into the disease RP. But even though they all go under the name RP, the diseases are caused by different mutations, the inheritance is different and also their progression vary and can give rise to substantially different problems with the retina and vision. (Sohocki et al., 2000)

Basic genetics

The canine genome has 39 chromosome pairs including X and Y, it has 2.4 gigabasepairs and about 19,000 genes (Yang et el., 1999) This can be seen in relation to the human genome that has 46 chromosomes, 3.0 gigabases and 21,000 genes. The sequencing of the canine genome in 2005 has opened up big opportunities for identification genes for diseases (Ofri & Narfström, 2007). When the mutations responsible for human retinopathies are known, orthologs in dogs can be identified as candidate genes.

Dogs have a unique population structure with many separate breeds constructed during a relatively short time. To date there are about 400 specific breeds, almost all of them originate from the last two centuries and now with closed herd books that stops gene exchange between breeds (Kirkness et al., 2003). There is evidence that dogs has lived together with humans for at least 15.000 years, but probably they have been in the surroundings of humans for much longer time, perhaps over 100.000 years (Vila et al., 1997). Selection in various traits, such as herding, hunting and guarding, have been made for a long time. Most of the breeds today have been "constructed" by a few founders who carried the specific physical and/or behavioural characteristics for the new breed. This together has made a big phenotypic variation between the breeds but a quite significant homogenization within the breeds. Genetic studies have given evidence of two major bottlenecks in dogs since they separated from the ancestral wolf (Lindblad-Toh et al., 2005). The domestication of the wolf as one and the cretion of the modern breeds as the other but other bottlenecks like the world wars could also have had influence.

The over 500 inherited diseases that are known in dogs could be used to research human disorders (OMIA, 2010). A majority of these diseases are also seen in humans and inheritance and clinical symptoms show high resemblance (Lindblad-Toh et al., 2005). As the frequency of specific diseases vary between different dog breeds this can suggest that a limited number of loci underlie each disease. The advantage of using animal models, and in this case dos is that it is easier to track genetic traits in a population with higher homogeneity than in an outbreed population, such as human families. Dogs share several of human diseases and the frequency varies among different breeds. (Mellersh et al., 2006) Animal models, for which the genetic basis have been studied and have the similar phenotypes with human diseases is valuable for therapeutic development.

Inherited retinal degeneration

Several species suffer from mutations that affect the development and function of the retina and were the retina becomes more and more degenerative (OMIA, 2010). For example the mutation in gene PRPH2, here described as Retinal degeneration type 2, is found in fish (danio), chicken, cattle, mouse, rat and a couple of other species (NCBI, 2013). In retinopathies the photoreceptors (cones and/or rods) in the retina gradually degenerate by apoptosis and lead to loss of vision (Pagon & Daiger, 2000; Phelan & Bok, 2000).

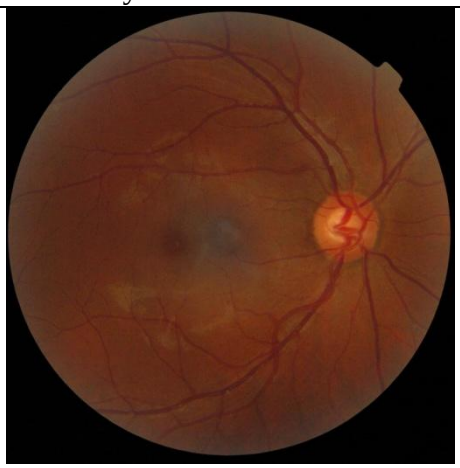
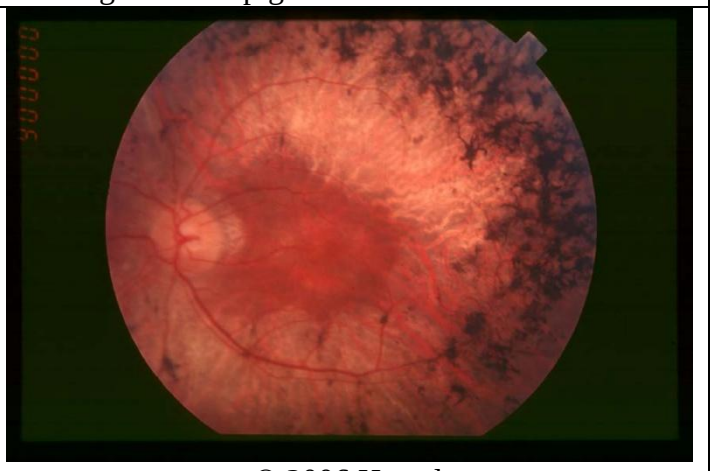
The first described case of PRA in dogs were in the early twentieth century (Parry, 1954) and today more than 100 breeds have had cases of retinal degeneration (Ofri & Narfström, 2006). Before the more advanced equipment and research methods that are available today almost all diseases that affected the retina and gave progressive vision losses and blindness was called PRA. This mainly because of the simplicity of grouping diseases with similar symptoms together and also because that before gene tests there were not much that could separate the diseases from each other. So even if the different genetic causes to the degeneration of the retina vary, the phenotypic symptoms could be very similar. Today there are much more precise diagnostic methods and genetic studies have made it clear that there are different underlying mutations that causes different diseases but give rise to similar phenotypes. Even the same disease, caused by the same mutation could have difference in clinical symptoms, such as onset and progression. It is found that 34 dog breeds have problem with this and it has occurred in over 100 breeds. In a review from 2009 it has shown that PRA and underlying related diseases is caused by 15 different mutations in 11 genes (Miyadera et al., 2009). Lots of research is going on in PRA due to the fact that dogs can be used as animal model for the human disease RP. RP are affecting 1 in 3,000 to 5,000 people and in dogs the frequency varies between the breeds (Haim, 2002).

In RP and PRA the photoreceptic rods degenerate first but there are also diseases when the cones degenerate first. In cone-rod dystrophies the visual impairment starts with day blindness (Mellersh et al., 2006).

Retinitis pigmentosa and Progressive retinal atrophy

The diseases RP and PRA are described as “rod-cone dystrophy” because the dysfunction of the retinal photoreceptors start with the rods in a later stage the cones (Pagon & Daiger, 2000). Some forms of RP onset in early childhood and others first in the midlife (Phelan & Bok 2000). The progression of RP varies and generally it can be seen that forms of RP that debut early also progress faster (Tuntivanich, 2009).

In the first stage when the rods start to degenerate it give rise to a slower adaptability to differences in dark and light and also loss of night vision. First in a later stage the cones start to degenerate and lose their function, it is first at this stage that visual impairment also occurs in daylight and the peripheral vision become affected and gives a tunnel vision. Sometimes even dark spots can arise in the central vision area.

Normal eye	Mid stage retinitis pigmentosa
	
© http://en.wikipedia.org	© 2006 Hamel

The first stage is often not noticed. Individuals often just are thought about as a bit clumsy in dusk and at nights but not more than that, perhaps they avoid driving when it is dark but show no more significant symptoms (Hamel, 2006; Pagon & Daiger, 2000; Phelan & Bok, 2000). In dog breeds that are known to have PRA dogs are regularly examined with ophthalmoscope to find pathological changes in the retina. (SKK/hälsa, 2013)

The cause of RP is due to different mutations in several different genes (OMIM, 2010). The mutations are on different chromosomes and as the loci vary the inheritance vary.

Types are:

- Autosomal dominant
- Autosomal recessive
- X-linked recessive
- X-linked dominant
- Other unusual forms: Y-linked inheritance, Digenic (double heterozygosity) and Syndromic mitochondrial form

In 2007 there were 30 different gene tests to diseases the retina of dogs (Ofri & Narfström, 2007)

In humans several other syndromes also associate with pigmentary retinopathies, such as Uscher syndrome (special type of deafness), metabolic diseases, renal abnormalities and neurological diseases (Hamel, 2006). A reason for this could be that the cause for RP often is a mutation that affect a protein coding sequence and that the protein is important to other functions in other cells.

Progressive retinal dysplasia

List of diseases that are included in this literature review.

Tabell 1					
Nr	**Disease**	**Inher-itance**	**Associated Genes**	**Chr**	**Human homologue**
1	**Achromatopsia, type 3, cone degeneration**	ar	CNGB3	29	Achromatopsia 3
2	**Cone-rod dystrophy, type 1**	ar	CORD1	15	RP
3	**Cone-rod dystrophy, type 2**	ar	NPHP4	36	Nephrocystin 4, RP combined renal disease
4	**Photoreceptor dysplasia**	ar	PDC	7	RP
5	**PRA autosomal dominant**	ad	RHO	20	dominant RP
6	**PRA rod-cone dystrophy, type 1**	ar	PDE6B	3	RP
7	**PRA rod-cone dystrophy, type 2**	ar	RD3	1	RP
8	**PRA rod-cone dystrophy, type 3**	ar	PDE6A PDE6B	3, 4	RP
9	**PRA X-linked**	X-linked	RPGR	X	X-linked RP
10	**Retinal degeneration, early**	ar	SHARP1	27	RP
11	**Retinal degeneration, type 2**	ar	PRPH2	12	RP
12	**Retinal pigment epithelial dystrophy**	ar	RPE65	6	RP
13	**Retinopathy, multifocal**	ar	BEST1	18	Macular dystrophy
14	**Rod-cone degeneration, progressive**	ar	CA4	9	RP
15	**Rod-cone dysplasia**	ar	GNGT2	9	dominant RP

1: CNGB3 Canine cone degeneration

CNGB3 cyclic nucleotide gated channel beta 3 [Canis lupus familiaris *]*
The gene is 782 amino acids long, protein coding gene located on chromosome 29 (uniprot 2011). It form a G-protein that activates by cGMP which open the cation channel and gives a depolarization of rod photoreceptors essential for generation of light-evoked electrical responses in the green-, red- and blue sensitive cones.

Canine cone degeneration (cd) is a congenital, autosomal recessively inherited disorder (Sidjanin et al., 2002). The responsible gene has shown to be CNGB3, a. Phenotype in

humans is a disease called achromatopsia-3 and the orthologous gene in humans is on chromosome 8 (Kohl et al., 2000). Both in dogs and humans the disease is congenital or onset early. Clinical signs in puppies are normally seen from 8 to 10 weeks of age (Seddon et al., 2006).
Canine cone degeneration has been found in the breeds Alaskan Malamute and German Shorthaired Pointer. (Sidjanin et al., 2002) The mutation makes the retinal sensory neurons unable to generate an electrical impulse to light and give rise to day-blindness. The breeds have different mutation in the region that leads to the disease. Alaskan Malamute disease is due to a deletion, size still not known but the study of Sidjanin et al. (2002) predicts it to be over 140 kb and in German Shorthaired Pointer it is due to a substitution in exon 6 of CNGB3. The homology between CNGB3 and ACHIM3 makes it a validated animal model.

2: CORD1 Cone-Rod Dystrophy (cord)

Cone-Rod dystrophy is not grouped together with RP and PRA as it is the cones to degenerate first. (Mellersh et al., 2006). The affected gene is homologue to the human gene RPGRP1 ("Retinitis pigmentosa GTPase regulator-interacting protein 1 gene) (Ensemble, 2011). It is mapped to a region on the 15:th chromosome in the dog genome in a area synthetic of a region on the 14:th chromosome in humans. The function of the normal gene is a key component in the photoreceptor protein and regulates the development of cones and rods. The mutation on the gene is an insertion that causes a frameshift and a premature stop codon. Causes a are detectable in puppies by ophthalmoscope examination at approximately 6 month of age
In humans this mutation causes an early and severe form of retinal dystrophy. Blindness or severe visual impairment often occurs already in childhood.
Cord is recessive inherited and mainly miniature longhaired dachshund is affected but the mutation has also been found in other breeds, such as English Springer Spaniel, Lhasa Apso, Miniature Schnauser, Newfoundland and Beagel (Miyadera et al. 2009). The mutation in miniature longhaired dachshund is stated to be a homologue to a human variant of RP and could be used as an animal model (Mellersh et al., 2006).

3: NPHP4 Cone-Rod Dystrophy, type 2

The gene Nephroretinin-4 (NPHP4) is located on the 5:th canine chromosome and the mutation is a 180-bp-deletion (Wiik et al., 2008). It codes for a protein involved in renal tubular development and function. This protein interacts with nephrocystin and is important for the normal development of the nephrones in the kidneys it also effect the actin- and microtubule-based structures and it is also found in the retina and if the protein is not function normally the photoreceptors are not function either (Roepman et al., 2005). Humans with a mutation in NPHP4 the symptoms are often both renal dysfunction and RP. Eventhough mutations in NPHP4 affect the nephrones and humans often have problems with the kidney as the main symptom and blindness as a "side effect", dogs doesn't seem to have the problem with the kidneys at all. Known affected breeds are standard wire-haired dachshund, miniature long-haired dachshund and pit bull terrier (Kijas et al., 2004; Mellersh et al., 2006). In the affected dachshund have the connection between kidney failure and vision loss not been seen (Wiik et al., 2008)

4: PDC Photoreceptor dysplasia

The gene PDC (phosductin) is on the 7:th canine chromosome and said to cause progressive photoreceptor dysplasia. (Zhang et al., 1999; OMIA, 2010) The gene is involved in the metabolism of the photoreceptors segment it is involved in changes in the phosphorylation of the protein due to light changes. (Uniprot, 2012) The dog breed mainly affected is miniature schnauzer. It is inherited autosomal recessive and is due to a C-to-G transversion within the PDC-gene. (Zhang et al., 1999) The disease onset early and affect both rod and cone photoreceptors. In a study from 2008 (Jeong et al.) a population of miniature schnauzer in Korea was examined and there were no evidence that a mutation in PDC causes photoreceptor dysplasia. It was shown that the disease was about the frequency in dogs with normal PDC and mutants and its role in the disease is questioned.

5: PRA – autosomal dominant

This form of PRA is caused by a mutation in Rhodopsin gene (RHO) (Kijas et al., 2002). Rhodopsin works as an G-protein receptor to induce the pathway for lightsensitivity. (Uniprot, 2012) The visual phototransduction is a multi-chain reaction that starts with photons reaching the retina in the eye is transformed into visual pigment that could be processed in the brain. (Wikipedia, 2012) In this process the rhodopsin is present in the rod shaped photoreceptor cell and required for image-forming vision in dusk or very low light. (Uniprot, 2012) The form has been identified in the breed English Mastiff. The disease seems to progress slowly in dogs. Rhodopsin is the visual pigment in rod photoreceptors and in human population mutations in RHO gene causes several different types of RP and also congenital night blindness (Retnet, 2010). The mutation is a missense mutation, C-to-G, causing a change from a Tyrosine to an Arginine (Kijas et al., 2002). Mutations in RHO-gene accounts for 30-40 % of RP with autosomal dominant inheritance in humans (Retnet, 2010).

6: PRA cone-rod dystrophy, type 1

Rod-cone dystrophy is caused by a nonsense mutation in PDE6B gene causing a premature stopcodon (Suber et al., 1993). The disease in mainly affecting Irish setter breeds. The gene in its functional form gives a protein that are involved in the procedure for amplification of the visual signal therefor it is necessary for the development of an efficient phosphodiesterase holoenzyme. (Uniprot, 2012)

7: PRA cone-rod dystrophy, type 2

Rod-cone dystrophy has yet only been found in collie breeds and is inherited autosomal recessive. (Kukekova et al., 2009). As in other rod-cone diseases the rod degenerate first and give rise to a slow adaptability to dull light and night blindness but clinical signs can be seen by ophthalmoscope examination when the puppies are about 3.5-4 month of age. Already at the age of 6-8 month the dogs can have become completely blind.
The RD3 gene is located at the 7:th chromosome in dogs and in 1:th in humans.

8: PRA cone-rod dystrophy, type 3

In this disease it is a mutation in the PDE-gene that leads to vision losses. PDE stands for phosphodiesterase and plays a role in the activity in the enzyme cGMP-specific PDE (cyclic guanosine monophosphate specific phosphodiesterase) (Dekomien, 2000). Phosphodiesterases

catalyse the hydrolyse of phosphate bonds in cAMP and cGMP they are there for highly involved in the regulation of the levels of second messenger in the cells. (Tocris, 2012) There are 11 subtypes of PDE which are distributed in different tissues and have different target, some cAMP, some cGMP and some both. The mutations found in dogs are in both PDE6A and PDE6B are inherited autosomal recessive (Tuntivanich, 2009; Dekomien, 2000). The disease this mutation causes in generalised progressive retinal atrophy (gPRA) in dogs and to the homologous disease retinitis pigmentosa (RP) in humans.

In the breed Welsh Corgi Cardigan it has shown that the mutation is a 1 bp deletion in PDE6A that causes a frame shift which leads to a premature stop codon and the disease. Dogs have shown to fail to develop normal rod-responses (Tuntivanich, 2009). The rod cells in the retina degenerate due to apoptosis which makes the vision impair. In the study of Tuntivanich et al. (2009) puppies with the mutation in PDE6A showed already from 17 days of age an significant reduced response in an test of react ability in the retina in compare to puppies without mutation. The same study state that both rods and coned is affected but it is the rods that first degenerate and then followed by the cones.

For PDE6B it has been shown that the mutation in the beta unit is caused by a transition providing a premature stop codon. (Suber et al., 1993) The mutation affects the cGMP-specific PDE in such way that rod PDE is totally absent. One other study by Dekomien et al. (2000) show that the mutation the dog breed Sloughi has in PDE6B, is due to an 8-bp insertion

9: PRA X-linked

X-linked RP is one of the most severe forms of RP (Guyon et al., 2007). The form of RP onset early and the vision losses progress fast. Studies have shown two different mutations in the RPGR-gene on the X-chromosome that leads to the degeneration of rods and cones. In Siberian husky and Samoyed dogs the mutation is due to micro deletion causing a premature stop codon causing XLPRA1 and in mixed breeds it is a frame-shift mutation causing XLPRA2. In humans mutations in the PRGR-gene account for 8-20% of RP cases in Europe and North America.

The gene is involved in the cilia and the formation of these. (Uniprot, 2012) Normal function in RPGR is not needed for development of the retina but is needed for maintenance and viability of the photoreceptors.

10: Early retinal degeneration

Early retinal degeneration onset as the name predict early and easily called the Erd-disease. The gene responsible, SHARP1, has been localized on the 27:th chromosome (Kukekova et al., 2003). The disease onset early and dogs become totally blind of a age between 12 to 18 month. Both rods and cones and their inner and other segments show abnormalities already during the postnatal retinal development and both cones and rods degenerate in about the same speed. The Erd-disease is found in the Norwegian elkhound breed.

11: Retinal degeneration, type 2

Retinal degeneration or generalised progressive retinal atrophy (gPRA) is a heterogen group. Different forms of hereditary have been distinguished and the cause is a combination of

mutations in peripherin 2 (Runte et al. 2000). Peripherin 2 is important for the normal development of the retina and in different breeds there are different mutations that cause disease. Peripherin is a glycoprotein in the membrane and serves as an adhesion protein that stabilises outer segment disks.

12: Retinal pigment epithelial dystrophy

This disease is congenital and gives up rise to night blindness (OMIA, 2010). The only know breed to be affected is Briard. RPE65 is a 65-kDa retinal pigment epithelium-specific protein. It is located on the 6: th chromosome and homologous diseases in human are RP and a congenital form of RP. The function of RPE65 is not fully known despite studies on RPE65-deficient knockout mice, but mutations in the gene leads to several retinal diseases, such as LCA, RP and retinal dystrophy (Dekomien, 2003).

13: Retinopathy, multifocal

The disease is due of a mutation in the gene Bestrophin and there is two mutations identified (Guziewicz et al., 2007). The gene is a 68-kDa plasma membrane protein expressed in retinal pigment epithelial cells Phenotypes in human are best macular dystrophy, which in humans are inherited dominant and in dog recessive. This retinopathy appears in multiple dog breeds. Characteristics for the disease is a late onset and a slow progress with degeneration of rods leading to severe damaged vision

14: Rod-cone degeneration, progressive

Progressive rod-cone degeneration (prcd) is due of a mutation in the gene carbonic anhydras IV (CA4), a protein coding gene on the 9:th chromosome (OMIA, 2010). The phenotype of the disease is typical for RP; with rods degenerate first and later on the cones (Zangerl et al., 2006). This disease onset late, with a broad span from 3 to 13 years of age. Normally are vision relative functional until age about 6 year. The mutation is spread in at least 20 breeds. There is a gene-test available that the Svedish Breeding Society (SKK) demands to be done before debute in breeding in some breeds; Pudel, Swedish Lapphund and some if the Spaniel and Retrever breeds (SKK/avel).

15: Rod-cone dysplasia

A G-protein; guanine nucleotide binding protein (GNGT2) on the 9: th chromosome has been associated with this disease but in a study by Akhmedov et al. (1998) evidence for this could not be established. The equivalent disease in humans is a dominant inherited form of RP.

Discussion

The function of the vision is complex and depend on that several genes make their protein just as intended. Mutations that lead to small changes in protein function can give rise to impaired vision and complete blindness. Diseases in the retina are as shown to be very heterogenic, they could have a slow or fast progress and could also affect different type of vision, like only night vision or total blindness. As dogs population structure is build up, they are breeding only within breeds, have a history with bottlenecks, many breeds have few founders and during 20-th century often with a certain amount of inbreeding their gene structure makes them excellent for usage of research on diseases that also affects humans. Loosing vision, one

of our senses is a severe handicap for the affected and the one around that individual. For the animal it can be result in euthanization in young years and for humans' lots of problems in the daily life. Could the genetic causes be determined and a gene therapy develop many lives would be richer.

Retinal atrophies in dogs are caused by mutations in, at least 12 genes, what are known today, and mutations in these genes are also known in humans. The genes that are mutated lack in function in some way that makes the retina to degenerate. Often is it a protein that is not develop as meant or not at all. Could the knowledge in dogs be uses in research of human diseases many people could be helped to a better life? For example when it is a gene for a protein regulating enzyme that is not functioning gene therapy could reinsert cells with normal function to stimulate the production. The cost of gene therapy would probably be to expensive for dogs but perhaps worth it for humans. In dogs could instead gene test lead to a change over generations, as individuals carrying a mutation for PRA would be excluded from breeding. This have been done successful for night blindness in Briard, were the disease was erased from the Swedish Briard-population in only a two of generations. When the gene-test was available the SKK decided that only individuals free from the mutation could be mated with heterozygote carriers for the disease and in the next generation all the heterozygote carriers also would be excluded from breeding. This way of erasing a disease is both fast and effective but there is always the question if the breed can afford loosing the genetic material from the excluded dogs. Is the population small and a bigger amount affected, then there are instead a risk of more inherited diseases to accumulate.

Even before gene tests are available for all different PRA-diseases much can be done in breeding to minimize the risk of spreading the disease to a bigger part of the population. And if the methods to test for the disease get better, more can be done to prevent spreading. The type of inheritance affects the actions that should be considered as breeding strategies to lower the risk of spreading the disease. The methods to early find carriers, wild types and mutants open if valid gene-tests develop. Breeding strategies could be applied on dogs but most likely not in humans, but gene test can be used in families predisposed for RP to give people a choice before they get children.

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