Congenital Ichthyosis

Congenital ichthyosis is a skin disease that is common among dogs of the **Golden Retriever** breed. The disorder is characterized by the excessive scaling of skin, often visible at a few weeks of age. The scales may persist throughout the animal's life and progressively blacken. Infectious complications are occasionally associated with the condition. The age of onset and clinical symptoms of the condition may vary in large scale.

Congenital ichthyosis in Golden Retrievers is caused by a **mutation in PNPLA1 gene** [1]. The mutation leads to the presence of a premature stop codon, resulting in the synthesis of a truncated protein which is assumed to be biologically inactive or has an altered biological activity. The disease is inherited in an **autosomal recessive** pattern [1].

References:

1. Grall A, et al. PNPLA1 mutations cause autosomal recessive congenital ichtyosis in golden retriever dogs and humans. Nature Genetics. 2012:44(2); 140-147.

Indications for genetic testing:

1. Carrier testing prior to breeding
2. Testing for affected dogs

Dry Eye and Curly Coat Syndrome

Dry eye and curly coat syndrome (**Congenital keratoconjuctivitis sicca and ichthyosiform dermatosis**) is found in **Cavalier King Charles Spaniels**. The disease affects the eyes and skin. Eye conditions are characterized by failure of tear production resulting in conjunctivitis, corneal ulceration and blindness. Skin disorder includes curly or rough coat, hyperkeratinization of glabrous skin and footpads.

The disease is associated with a single base **deletion in the gene FAM83H**. The disease has autosomal recessive inheritance.

Indications for genetic testing:

1. Carrier testing prior to breeding
2. Testing for affected dogs

Episodic Falling Syndrome

Episodic falling syndrome (EFS) (also known as “sudden collapse”) is canine paroxysmal hypertonicity disorder found in **Cavalier King Charles Spaniels**.

Episodes are induced by exercise, stress or excitement and characterized by progressive hypertonicity throughout the thoracic and pelvic limbs. Typical sign of the disorder is temporary inability to relax the affected limb and trunk muscles. The age of onset is between three and seven month of age, and affects both male and female dogs.

EFS is caused by 15.7 kb **deletion in the BCAN gene** encoding the brain-specific extracellular matrix proteoglycan brevican. The disease is inherited in an autosomal recessive manner.

Indications for genetic testing:

1. Carrier testing prior to breeding
2. Testing for affected dogs

Exercise-Induced Collapse

Exercise-induced collapse (EIC) is a life-threatening condition most commonly affecting **Labrador retrievers**. The disorder in dogs is characterized by muscle weakness, loss of control of the limbs and lack of coordination after intense exercise. If the exercise is continued, the dogs usually collapse. The symptoms of the disease commonly appear as dogs enter in strenuous training, however dogs may not develop any symptoms depending on their lifestyle.

EIC has been associated with a mutation in **DNM1 gene**. A single nucleotide substitution results in the conversion of arginine to leucine (p.Arg256Leu) [1]. The carrier frequency of this mutation has been estimated as high as 37% in some **Labrador retriever** populations. Also, this mutation has been detected in other EIC affected dogs including **Curly-Coated and Chesapeake Bay Retrievers, Boykin Spaniels, Bouvier des Flanders, German Wirehaired Pointers, Old English Sheepdogs, Cocker Spaniels** and **Pembroke Welsh Corgis**. The pattern of inheritance is autosomal recessive.

References:

1. Patterson EE, Minor KM, Tchernatynskaia AV, et al. A canine DNM1 mutation is highly associated with the syndrome of exercise-induced collapse. Nat Genet. 2008 Oct;40(10):1235-9.

Indications for genetic testing:

1. Carrier testing prior to breeding
2. Testing for affected dogs

Multi-Drug Resistance

Several **drugs** such as **ivermectin, doramectin, loperamide, vincristine, vinblastine** and**doxorubicin** that are used in the treatment of dogs may induce serious side-effects. It has been described that several dog breeds are more prone to side-effects from these drugs. In dogs with genetic predisposition, the underlining cause of this drug sensitivity is a mutation in **MDR1 gene** [1,2].

MDR1 protein is a drug transporter. The 4-bp deletion in MDR1 gene results in a frameshift in protein translation leading to a premature stop codon [1]. The defective protein has reduced drug elimination ability and the accumulation of toxins occurs. Exposure to certain drugs in dogs with MDR1 mutation may result in serious neurological symptoms including seizures, ataxia, blindness and death.

MDR1 mutation has been found in **Australian Shepherd**, **Collie, Long-haired Whippet, McNab, Silken Windhound** and several other breeds [3].

References:

1. Mealey, K.L., et al. (2001) Ivermectin sensitivity in collies is associated with a deletion mutation of the mdr1 gene. Pharmacogenetics, 11, 727–733.

2. Mealey, K.L., et al. (2003) Increased toxicity of P-glycoprotein-substrate chemotherapeutic agents in a dog with the MDR1 deletion mutation associated with ivermectin sensitivity. Journal of the American Veterinary Medical Association, 223, 1453–1455

3. Gramer, I. et al. (2011). Breed distribution of the nt230(del4) MDR1 mutation in dogs. Vet J. 2011 Jul;189(1):67-71.

Indications for genetic testing:

1. Carrier testing prior to breeding
2. Testing for affected dogs

Primary Lens Luxation

Primary lens luxation (PLL) is a potentially blinding genetic ocular disorder in dogs, particularly in **terrier** and **terrier-type breeds**. The disease is characterized by the rapid displacement of lens from its normal location in the eye. Although the first symptoms of the condition can be detected at around 20 months of age, the lens luxation occurs between 3 to 8 years depending on the breed [1].

To date, only one mutation in **ADAMTS17 gene**has been associated with PLL in dogs. This single nucleotide substitution (c.1473+1G>A) in intron 10 causes the skipping of exon and frameshift resulting in a premature termination codon that is predicted to lead to a truncated protein [2]. The disease is inherited in an autosomal recessive pattern.

The most commonly affected breeds are terriers, however, the mutation has also been found in other PLL- affected dogs including **Australian Cattle dog, Chinese Crested, Jagdterrier, Parson Russell terrier, Patterdale terrier, Rat terrier, Sealyham terrier, Tenterfield terrier, Tibetan terrier, Toy Fox terrier, Volpino Italiano, Welsh terrier, Wire-haired Fox terrier, Yorkshire terrier**[3].

References:

1. Curtis R, Barnett KC, Lewis SJ. Clinical and pathological observations concerning the aetiology of primary lens luxation in the dog. Veterinary Record 1983; 112: 238–246.

2. Farias FH, Johnson GS, Taylor JF et al. An ADAMTS17 splice donor site mutation in dogs with primary lens luxation. Investigative Ophthalmology and Visual Science 2010; 51: 4716–4721.

3. Gould D, Pettitt L, McLaughlin B, et al. ADAMTS17 mutation associated with primary lens luxation is widespread among breeds. Vet Ophthalmol. 2011 Nov;14(6):378-84.

Indications for genetic testing:

1. Carrier testing prior to breeding
2. Testing for affected dogs

Primary Open Angle Glaucoma

Primary open angle glaucoma (POAG) is a genetic disorder that is characterised by increased intraocular pressure leading to optic nerve and retina damage and resulting in partial or complete blindness. Symptoms of POAG include painful eyes, red and dilated pupils, cloudy cornea, as well as behavioural changes with loss of appetite, eye scratching and apathy. In affected dogs, the first symptoms of the disease begin at 8 to 16 months of age [1].

The prevalence of POAG in **Beagle dogs** is around 1% [2]. The disease in Beagles is caused by a single nucleotide substitution in **ADAMTS10 gene** [1]. This mutation results in the substitution of glycine to arginine (p.Gly661Arg) and has a deleterious effect on protein function [1]. To date, ADAMTS10 mutation has not been observed in POAG-affected breeds other than Beagles [3]. The disease is inherited in an autosomal recessive pattern.

POAG is treatable, however, the success of the treatment depends largely upon the time of the diagnosis. Genetic testing of ADAMTS10 mutation in Beagles enables the identification of dogs with high risk for developing POAG prior to the manifestation of clinical symptoms.

References:

1. Kuchtey J, Olson LM, Rinkoski T, et al. Mapping of the disease locus and identification of ADAMTS10 as a candidate gene in a canine model of primary open angle glaucoma. PLoS Genet. 2011;7:e1001306.
2. Gelatt KN, MacKay EO. Prevalence of the breed-related glaucomas in pure-bred dogs in North America. Vet Ophthalmol. 2004;7:97–111.
3. Kuchtey J, Kunkel J, Esson D, et al. Screening ADAMTS10 in Dog Populations Supports Gly661Arg as the Glaucoma-Causing Variant in Beagles. Invest Ophthalmol Vis Sci. 2013 Mar 13;54(3):1881-6.

Indications for genetic testing:

1. Carrier testing prior to breeding
2. Testing for affected dogs

Progressive Retinal Atrophy – GR-PRA1

Progressive retinal atrophy (PRA) in dogs is characterized by the degeneration of the retina, causing progressive vision loss leading to complete blindness. The first clinical symptom of the disorder typically includes night blindness due to the degeneration of rod cells that are essential for night vision. At later stage of the disorder, the cone cells are damaged, gradually affecting the sight during the daylight. The disease results in complete blindness in the affected animal [1]. Several forms of PRA have been described in more than 100 dog breeds. While the clinical symptoms of different forms of PRA are similar, the etiology, age of onset and the rate of progression vary.

Several forms of PRA are described in the **Golden Retrievers**, including the prcd-PRA, GR-PRA1 and GR-PRA2. **GR-PRA1** is caused by a **mutation in SLC4A3 gene** [2]. The disease occurs due to a single nucleotide insertion causing a frameshift resulting in a premature termination codon. The frequency of the mutant allele is approximately 2% to 6% among the Golden Retrievers in Europe. GR-PRA1 has an average age of onset at approximately 7 years. The disease is inherited in an **autosomal recessive** pattern.

References:

1. Dostal J, et al. Progressive rod-cone degeneration (PRCD) in selected dog breeds and variability in its phenotypic expression. Veterinarni Medicina, 2011:56(5); 243-247

2. Downs, et al. A frameshift mutation in golden retriever dogs with progressive retinal atrophy endorded SLC4A3 as a candidate gene for human retinal degenerations. PLoS ONE 2011:6(6); e21452

Indications for genetic testing:

1. Carrier testing prior to breeding
2. Testing for affected dogs

Progressive Retinal Atrophy – GR-PRA2

Progressive retinal atrophy (PRA) in dogs is characterized by the degeneration of the retina, causing progressive vision loss leading to complete blindness. The first clinical symptom of the disorder typically includes night blindness due to the degeneration of rod cells that are essential for night vision. At later stage of the disorder, the cone cells are damaged, gradually affecting the sight during the daylight. The disease results in complete blindness in the affected animal [1]. Several forms of PRA have been described in more than 100 dog breeds. While the clinical symptoms of different forms of PRA are similar, the etiology, age of onset and the rate of progression vary.

Several forms of PRA are described in the **Golden Retrievers**, including the **prcd-PRA**, **GR-PRA1** and**GR-PRA-2**. Geneticists at the Animal Health Trust and scientists at the Swedish University of Agricultural Sciences and Uppsala University have identified a recessive mutation that causes a form of PRA in the Golden Retriever, known as **GR-PRA2**.

According to Animal Health Trust (www.aht.org.uk), the GR-PRA2 accounts for approximately 15% of known PRA cases in the breed. GR-PRA1 and GR-PRA2 in combination with the prcd-PRA test, identifies nearly all causes of PRA in the breed. Although, there are still a few cases of PRA in the golden retriever that are caused by unidentified mutations.

References:

1. Dostal J, et al. Progressive rod-cone degeneration (PRCD) in selected dog breeds and variability in its phenotypic expression. Veterinarni Medicina, 2011:56(5); 243-247

Indications for genetic testing:

1. Carrier testing prior to breeding
2. Testing for affected dogs

Progressive Rod-Cone Degeneration – prcd-PRA

Progressive rod–cone degeneration (prcd-PRA), a form of progressive retinal atrophy (PRA), is a canine genetic disease that is characterized by degeneration of the retina, causing progressive vision loss leading to blindness. PRA in dogs is considered as an equivalent to human retinitis pigmentosa (RP) and displays phenotypic as well as genetic similarity to this disease [1]. The first clinical symptom of the disorder typically includes night blindness due to the degeneration of rod cells that are essential for night vision. At later stage of the disorder, the cone cells are damaged, gradually affecting sight during the daylight. The disease results in complete blindness in the affected animal [2]. The disorder has been described in many dog breeds including **Labrador Retrievers**. In the **Golden Retrievers**, prcd-PRA, only accounts for a very small proportion of PRA cases. The age of onset of the disease and disease progression varies between the dog breeds; however, the clinical symptoms are first described usually in early adolescence or early adulthood.

Progressive rod-cone degeneration is caused by a **mutation in the PRCD gene** [1], where the substitution of nucleotide G to A in PRCD gene causes an amino acid change from cysteine to tyrosine in the translated protein. The disease is inherited in an **autosomal recessive** pattern.

References:

1. Zangerl B, et al. Identical mutation in a novel retinal gene causes progressive rod-cone degeneration in dogs and retinitis pigmentosa in humans. Genomics, 2006:88; 551-563

2. Dostal J, et al. Progressive rod-cone degeneration (PRCD) in selected dog breeds and variability in its phenotypic expression. Veterinarni Medicina, 2011:56(5); 243-247

Indications for genetic testing:

1. Carrier testing prior to breeding
2. Testing for affected dogs

X-Linked Progressive Retinal Atrophy

Progressive retinal atrophy (PRA) in dogs is characterised by the degeneration of the retina, causing progressive vision loss leading to complete blindness. The first clinical symptom of the disorder typically includes night blindness due to the degeneration of rod cells that are essential for night vision. At later stage of the disorder, the cone cells are damaged, gradually affecting the sight during the daylight. The disease results in complete blindness in the affected animal [1]. Several forms of PRA have been described in more than 100 dog breeds. While the clinical symptoms of different forms of PRA are similar, the aetiology, age of onset and the rate of progression vary.

The first clinical symptoms of **X-linked progressive retinal atrophy** (XLPRA) in dogs start to manifest around three to five years of age. Several types of XLPRA have been described:**XLPRA1** in **Siberian Huskies** and **Samoyeds** and **XLPRA2** in mongrel dogs [2] and **XLPRA3** in **Border Collies** [3].

XLPRA1 is caused by a five nucleotide deletion in **RPGR gene**leading to a premature stop codon resulting in a truncated protein [2]. XLPRA2 is caused by a GA deletion in the same RPGR gene. The causative mutation of XLPRA3 has not been determined [3].The disease has an X-linked inheritance pattern [2].

References:

1. Dostal J, et al. Progressive rod-cone degeneration (PRCD) in selected dog breeds and variability in its phenotypic expression. Veterinarni Medicina, 2011:56(5); 243-247.
2. Zhang Q, et al. Different RPGR exon ORF15 mutations in Canids provide insights into photoreceptor cell degeneration. Hum Mol Genet. 2002 May 1;11(9):993-1003.
3. Vilboux T, et al. Progressive retinal atrophy in the Border Collie: a new XLPRA. BMC Vet Res. 2008 Mar 3;4:10.

Indications for genetic testing:

1. Carrier testing prior to breeding
2. Testing for affected dogs