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PROGRESS IN GENETIC RESEARCH INTO THE DETECTION OF INHERITED EYE DISEASES

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Inherited eye diseases are common in purebred dogs. Conditions range from simply inherited disorders such as progressive retinal atrophy to disorders that are likely to have a more complex mode of inheritance, such as entropion. Advances in canine molecular genetics has led to the identification of gene defects underlying some inherited eye disorders and have allowed the development of DNA-based tests to enable breeders to eradicate the conditions by selective breeding.

Cataract

Mutations in the HSF4 (heat-shock transcription factor 4) gene have been identified as causing juvenile cataracts in the Staffordshire Bull Terrier, Boston Terrier and Australian Shepherd.¹

Collie Eye Anomaly

The gene for choroidal hypoplasia (CH; the diagnostic lesion of collie eye anomaly) was been mapped to chromosome 37² and apparently subsequently identified (www.Optigen.com), although this has not yet been published. However a DNA test for CH is available.

Retinal Dysplasia

Recently an abnormality of expression of mitochondrial DNA was discovered in miniature schnauzers with retinal dysplasia.³ In the miniature schnauzer retinal dysplasia has variable severity with some dogs having focal areas of retinal dysplasia and others being blind with retinal detachments. Some affected dogs also have persistent hyperplastic primary vitreous.⁴

Multifocal retinopathy

An autosomal recessive condition whereby multifocal serous retinal detachments develop in affected puppies at 3 to 4 months of age has been described in Great Pyrennes and Coton de Tulear dogs. The causal gene mutation has been identified and is in a gene called bestrophin (paper in press). The bestrophin gene is mutated in Best macular dystrophy, a juvenile-onset disease that affects the macular in humans.

Progressive retinal atrophy (PRA)

This is a very common group of conditions that can be inherited in an autosomal recessive, autosomal dominant or X-linked manner. The underlying gene mutations have been identified for a number of different forms. There is a range of ages of onset and rate of progressions. Classically PRA is considered as a rod-led retinal degeneration meaning the rod photoreceptors degenerate first and this is followed by degeneration of the cones. Rod death results in night blindness and when cones die

complete blindness results. Affected retinas are thinned (seen as tapetal hyperreflectivity) and retinal vasculature becomes attenuated. Forms with a cone-led degeneration are considered separately as cone rod dystrophies. Gene defects underlying several forms of PRA have been identified.

Rod Cone Dysplasia (*rcd*)

Mutations in two members of the rod phototransduction cascade cause *rcd*; the alpha (Cardigan Welsh Corgi) and the beta (Irish setter and Sloughi – same gene but different mutations) subunit of cyclic GMP phosphodiesterase, known as PDE6A and PDE6B respectively. The conditions are autosomal recessive. These are early-onset (in the breeds investigated) with a lack of normal rod development and function and very early night blindness. The age at which affected dogs go completely blind varies between breed. DNA-based diagnostic tests are available for all three breeds.

Progressive rod cone degeneration (*prcd*)

Numerically *prcd* is the most important form of PRA, with several different breeds being affected. It is inherited in an autosomal manner. The retina of affected dogs develops normally but then undergoes slow degeneration. The rate of onset varies considerably, particularly in certain breeds. The gene mutation was discovered in a gene that was previously unknown.⁵ Breeds affected include: American Eskimo Dog, Australian Cattle Dog, Australian Stumpy Tail Cattle Dog, Chesapeake Bay Retriever, Chinese Crested, Cocker Spaniel (American & English), Entlebucher Sennenhund, Finnish Lapphund, Labrador Retriever, Nova Scotia Duck Tolling Retriever, Poodle (Miniature & Toy), and Portuguese Water Dog. A DNA-based diagnostic test is available.

Dominant PRA

A dominantly inherited form of PRA occurs due to a mutation in the rhodopsin gene in Bull Mastiffs and Old English Mastiffs. The rate of retinal degeneration is increased by retinal exposure to light. A DNA-based diagnostic test is available.

X-linked PRA

X-linked PRA occurs in the Samoyed and Siberian Husky. They have different mutations in the same region of the same gene; the retinitis pigmentosa GTPase regulator (RPGR) gene. A DNA-based diagnostic test is available.

Cone Rod Dystrophies (*crd*)

Initially cones and then rods degenerate. *Crd* type 1 and 2 were identified in pit bull terriers, *crd3* in the Glen of Imaal.^{6, 7} The miniature longhaired dachshund (*crd4*) has a mutation in the gene RPGRIP1 (retinitis pigmentosa GTPase regulator-interacting protein).⁸ An additional form of cone-rod dystrophy has been described in the standard wire-haired dachshund.^{9, 10} One of the early features is that affected puppies develop pin-point pupils when examined with a focal light source. The rate of progression appears quite variable. The standard wire-haired dachshund with *crd* apparently does not have the same gene mutation as that described in the miniature longhaired dachshund (Berjkas personal communication, 2007).

Achromatopsia (Day Blindness)

Achromatopsia is a condition characterized by a lack of cone function but with normal rod function. Ophthalmoscopic examination is unremarkable in affected dogs.

Mutations in the cyclic nucleotide-gated channel beta-subunit gene (CNGB3) have been identified in Alaskan Malamutes and German Shorthaired Pointers.¹¹

Retinal Dystrophy/Leber Congenital Amaurosis of Briards

Affected dogs have poor day and especially night vision from an early age but only a very slow retinal degeneration. It is autosomal recessive and caused by a mutation in a gene called RPE65¹².

DNA-based genetic testing

DNA-based tests are very accurate in determining the genotype (the presence of a particular genetic feature) of any animal under test. Once a disease causing mutation is identified it is relatively easy to develop a test which will show whether any given animal has the disease causing mutation. Such a test will show if both copies of the gene are mutated, whether one of the copies is mutated and the other normal, or if both copies are normal. Obviously such a test is extremely valuable to breeders and allows them the opportunity of eradicating the disease in as little as one generation.

DNA tests are especially valuable for recessively inherited diseases, and those with a late age of onset. The occurrence of carriers of recessive disorders makes it very difficult to eradicate a disease without a DNA-based test for the mutation. With late onset disease an animal that is affected by the disease may have already been bred from before the signs of the disease appear.

Some recessively inherited genetic diseases have a high incidence in certain breeds. In these circumstances trying to avoid breeding from animals with the mutation can narrow the gene pool and cause additional problems in the breed; it may mean that desirable features are lost to the breed, or that a different genetic disease that was previously at low frequency in the breed becomes commoner and if there was no test for the new disease the breeders would be in a worse position than before the eradication attempt. For a recessive disease the most important thing is to ensure that no more affected animals are produced. Carriers that have outstanding features can still be used but must be mated with genetically clear animals to ensure that no affected offspring are produced. The same is true for actual affected animals, but generally these would only be used if they had some absolutely outstanding features that should be saved. Gradually, over a few generations as the desired features are separated from the undesirable features, the condition can be eradicated. This could be considered as a process of separating the "good" genes from the "bad" genes. Thus the aim of eliminating the disease can be achieved without causing damage to the breed as a whole.

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