10. Interpretation of genetic tests, known genes/mutations affecting vision and/or causing hereditary eye diseases in dogs and cats & Laboratories with molecular genetic testing capabilities

Interpretation of Genetic Tests

As veterinarians it is important that we are equipped to help owners/breeders interpret genetic tests. As a specialty there are more genetic tests in ophthalmology than in any other specialty.
DNA-based genetic tests are very specific – they only identify the gene mutation that they are designed for; and for conditions with genetic heterogeneity, such as PRA, this can be confusing. Each form of PRA is caused by a different gene mutation and requires a DNA-based test specific for it. It is important that the owner/breeder appreciates that testing clear for one form of PRA does not mean that the animal is clear for all forms of PRA. The fact that an individual animal is shown to be unaffected by a genetic test for one form of PRA and yet still develops PRA (caused by a different gene mutation) can be confusing and lead owners/breeders to question the validity of genetic testing. We need to play a role in helping with the interpretation of the results of genetic testing.

Which Laboratory to Use?
Utilizing a well-established laboratory is recommended. It is important that strict quality assurance is followed. DNA-based tests are very accurate if they are well designed, however there is always the possibility for human error. With good laboratory practices risk of such mistakes will be minimized. Some tests are subject to patent and laboratories breaking such patents should be avoided.

Samples for DNA-based tests
It is important to follow the sample collection and handling instructions for the laboratory running the DNA test. Although DNA can be obtained from many different types of sample (blood, cheek swab, hair plucking, semen sample etc) the test being run may be optimized for the quality of DNA obtained from one source (typically blood) and the laboratory may not wish to utilize another DNA source (such as cheek swabs). Accurate labeling of the sample is critical (particularly if multiple animals are being sampled) and steps should be taken to avoid contamination (particularly important if cheek swabs are being used).

Types of Test
Most DNA-based tests are mutation-detection tests.

Mutation-detection tests
For this form of test the DNA mutation that is believed to cause the disease being tested for has been identified. The test is designed to show the genotype of the animal which can be one of the following:

1. Homozygous for the normal allele at the site of the disease causing mutation – animal is genetically clear of the condition
2. Homozygous for the disease causing allele – animal will be affected with the condition (assuming complete penetrance)
3. Heterozygous for the disease causing allele. i.e. has one normal copy of the allele and one mutated copy. For recessive disease the animal will be phenotypically normal but will be a carrier of the condition. If the condition is dominantly inherited the animal will be affected.

Linked-marker tests

Occasionally a locus for a hereditary disease may be mapped and yet the mutation has not yet been identified. DNA-markers for the mapped region can be used for genetic tests until the actual causal gene mutation is identified. Such tests may be used to implicate which animals are likely to have the condition, or are likely not to have the condition. Linked-marker tests must be interpreted with caution.

Potential problems with genetic testing

- If the presumptive disease causing DNA mutation does not actually cause the condition. Robust peer-review of the evidence implicating the putative mutation should be obtained (i.e. publication of the mutation in the scientific literature).
- Design of test. A robust DNA-based test must be designed. Some tests are designed on whether or not a polymerase chain reaction product is produced (such as an allele-specific PCR tests). Such tests should be utilized carefully with appropriate controls. A result based on a lack of a PCR product is always of concern as there are many reasons that a PCR reaction may fail in addition to not having the allele being tested for.
- Standards within the laboratory running the test. Tests are typically based on polymerase chain reaction amplification of DNA. This can amplify product from very low amounts of DNA. It is important that both positive and negative controls are utilized in the laboratory and steps are taken to check that no contamination of samples or equipment occurs.
- Mix up of samples. This can occur at the time of collection or possibly (but hopefully not) in the laboratory.
- Genetic heterogeneity. As already mentioned this can lead to confusion if the owner/breeder is not well informed
- Phenocopies. This is an environmentally induced condition that mimics a genetic condition.

Known genes/mutations affecting vision and/or causing hereditary eye diseases in dogs and cats & Laboratories with molecular genetic testing capabilities

Breed	Disease	Gene	Laboratory
Abyssinian cat and multiple other cat breeds	arPRA *RdAc*	CEP290	Laboklin; CatDNAtest.org; UCDavis VGL
Abyssinian cat	adPRA *Rdy*	CRX	UCDavis VGL
Alaskan malmute	Cone degeneration (achromatopsia)	CNGB3	Optigen
American Bulldog	Neuronal ceroid lipofuscinosis	CTSD	MU
American Cocker Spaniel	arPRA - *prcd*	PRCD	Optigen
American Eskimo Dog	arPRA - *prcd*	PRCD	Optigen
American Pit Bull	crd2	?	Optigen
Australian Cattle Dog	arPRA - *prcd*	PRCD	Optigen
Australian Cattle Dog	Primary Lens Luxation	ADAMTS17	MU; vetGen; AHT
Australian Shepherd	CEA-CH	Intronic mutation in NEHJ1	Optigen
Australian Shepherd	Cone degeneration (achromatopsia)	CNGB3	Optigen
Australian Shepherd	Canine multifocal retinopathy type 1	BEST1	Optigen

Australian Shepherd	arPRA - *prcd*	PRCD	Optigen
Australian Shepherd	Hereditary Cataract	HSF4	AHT
Australian Shepherd	Neuronal ceroid lipofuscinosis	CLN6	MU
Australian Stumpy Tail Cattle Dog	arPRA - *prcd*	PRCD	Optigen
Beagle	Primary open angle glaucoma	ADAMTS10	Optigen
Border Collie	CEA-CH	Intronic mutation in NEHJ1	Optigen
Boston Terrier	Hereditary Cataract (early-onset form only)	HSF4	vetGen; AHT
Boykin Spaniel	CEA-CH	Intronic mutation in NEHJ1	Optigen
Briard	Congenital Stationary Night Blindness (CSNB)	RPE65	Optigen, AHT
Bull Mastiff	adPRA	rhodopsin	Optigen
Bull Mastiff	Canine multifocal retinopathy type 1	BEST1	Optigen
Cane Corso	Canine multifocal retinopathy type 1	BEST1	Optigen
Cardigan Welsh Corgi	arPRA – *rcd3*	PDE6A	Optigen
Cavalier King Charles Spaniel	Curly Coat Dry Eye	FAM83H	AHT
Chesapeake Bay Retriever	arPRA - *prcd*	PRCD	Optigen
Chinese Crested	arPRA - *prcd*	PRCD	Optigen
Chinese Crested	Primary Lens Luxation	ADAMTS17	MU; vetGen; AHT
Coton du Tulear	Canine multifocal retinopathy type 2	BEST1	Optigen
Dachshund	Neuronal ceroid lipofuscinosis	PPT1	MU
Dogue de Bordeaux	Canine multifocal retinopathy type 1	BEST1	Optigen
(English) Cocker Spaniel	arPRA - *prcd*	PRCD	Optigen
English & Bull Mastiff	Canine multifocal retinopathy type 1	BEST1	Optigen
English Setter	Neuronal ceroid lipofuscinosis	CLN8	MU
English Springer Spaniel	CORD1	RPGRIP1	AHT
Entlebucher Sennenhund	arPRA - *prcd*	PRCD	Optigen
Finnish Lapphund	arPRA - *prcd*	PRCD	Optigen
French Bulldog	Hereditary Cataract	HSF4	vetGen; AHT
Golden Retriever	arPRA - *prcd*	PRCD	Optigen
Golden Retriever	arPRA	SLC4A3	Optigen
Gordon Setter	Late-onset arPRA - *rcd4*	?	AHT
German Shorthaired Pointer	Cone degeneration (achromatopsia)	CNGB3	Optigen
Glen of Imaal Terrier	crd3	ADAM9	Optigen

Great Pyrenees (Pyrenean Mountain Dog)	Canine multifocal retinopathy type 1	BEST1	Optigen
Irish Red and White Setter	arPRA – *rcd1*	PDE6B	Optigen, AHT
Irish Setter	arPRA – *rcd1*	PDE6B	Optigen, AHT
Irish Setter	Late-onset arPRA - *rcd4*	?	AHT
Jack Russell Terrier	Primary Lens Luxation	ADAMTS17	MU; AHT
Jagdterrier	Primary Lens Luxation	ADAMTS17	vetGen; MU; AHT
Japanese Chin	GM2 gangliosidosis	HEXA	MU
Karelina Bear Dog	arPRA - *prcd*	PRCD	Optigen
Kuvasz	arPRA - *prcd*	PRCD	Optigen
Labrador Retriever	arPRA - *prcd*	PRCD	Optigen
Labrador Retriever	Ocular Skeletal Dysplasia (dwarfism with retinal dysplasia - Drd1)	CLO9A2	Optigen
Lancashire Heeler	CEA-CH	Intronic mutation in NEHJ1	Optigen
Lancashire Heeler	Primary Lens Luxation	ADAMTS17	vetGen; MU; AHT
Lapponian Herder	Canine multifocal retinopathy type 3	BEST1	Optigen
Lapponian Herder	arPRA - *prcd*	PRCD	Optigen
Long-haired Dachshund	Neuronal ceroid lipofuscinosis	TPP1	MU
Long-haired Dachshund	CORD1	RPGRIP1	AHT
Longhaired Whippet	CEA-CH	Intronic mutation in NEHJ1	Optigen
Markiesje	arPRA - *prcd*	PRCD	Optigen
Miniature Bull Terrier	Primary Lens Luxation	ADAMTS17	vetGen; MU; AHT
Miniature & Toy Poodle	arPRA - *prcd*	PRCD	Optigen
Miniature Schnauzer	arPRA – type A	Phosducin	Optigen
Miniature Long-haired & Smooth-haired & Wire-haired Dachshund	CORD1	RPGRIP1	MU; AHT
Miniature Wire-haired Dachshund	Cone rod dystrophy	NPHP4	AHT
Norwegian Elkhound	arPRA - *prcd*	PRCD	Optigen
Norwegian Elkhound	arPRA- *erd*	STK38L	not available
Nova Scotia Duck Tolling Retriever	CEA-CH	Intronic mutation in NEHJ1	Optigen
Nova Scotia Duck Tolling Retriever	arPRA - *prcd*	PRCD	Optigen
Old English Mastiff	adRPA	rhodopsin	Optigen
Old English Mastiff	Canine multifocal retinopathy type 1	BEST1	Optigen
Papillon	arPRA type 1	?	MSU

Parson Russell Terrier	Primary Lens Luxation	ADAMTS17	vetGen; MU; AHT
Patterdale Terrier	Primary Lens Luxation	ADAMTS17	vetGen; MU; AHT
Perro de Presna Canario	Canine multifocal retinopathy type 1	BEST1	Optigen
Portuguese Water Dog	arPRA - *prcd*	PRCD	Optigen
Rat Terrier	Primary Lens Luxation	ADAMTS17	vetGen; MU; AHT
Rough & Smooth Collie	*rcd2*	c1orf36	Optigen
Rough & Smooth Collie	CEA-CH	Intronic mutation in NEHJ1	Optigen
Samoyed	xlPRA	RPGR*	Optigen
Samoyed	Ocular Skeletal Dysplasia (dwarfism with retinal dysplasia - Drd2)	CLO9A3	Optigen
Schapendoes	arPRA	CCDC66	Bochum university
Sealyham Terrier	Primary Lens Luxation	ADAMTS17	vetGen; MU; AHT
Shetland Sheepdog	CEA-CH	Intronic mutation in NEHJ1	Optigen
Short-haired Dachshund	arCRD	NPHP4	NSVS
Siberian Husky	xlPRA	RPGR*	Optigen
Silken Windhound	CEA-CH	Intronic mutation in NEHJ1	Optigen
Silky Terrier	arPRA - *prcd*	PRCD	Optigen
Sloughi	arPRA – *rcd1a*	PDE6B	Optigen
Spanish Water Dog	arPRA - *prcd*	PRCD	Optigen
Staffordshire Bull Terrier	Hereditary Cataract	HSF4	vetGen; AHT
Standard Wire-Haired Dachshund	Cone rod dystrophy	NPHP4	AHT
Swedish Lapphund	arPRA - *prcd*	PRCD	Optigen
Tenterfield Terrier	Primary Lens Luxation	ADAMTS17	vetGen; MU; AHT
Tibetan Terrier	Primary Lens Luxation	ADAMTS17	vetGen; MU; AHT
Tibetan Terrier	Neuronal ceroid lipofuscinosis	ATP13A2	MU
Toy Fox Terrier	Primary Lens Luxation	ADAMTS17	vetGen; AHT
Volpino Italiano	Primary Lens Luxation	ADAMTS17	vetGen; MU; AHT
Welsh Terrier	Primary Lens Luxation	ADAMTS17	vetGen; MU; AHT
Wire-haired Fox Terrier	Primary Lens Luxation	ADAMTS17	vetGen; AHT
Yorkshire Terrier	Primary Lens Luxation	ADAMTS17	vetGen; AHT
Yorkshire Terrier	arPRA - *prcd*	PRCD	Optigen

***** the mutations in RPGR in the Samoyed and Siberian Husky are the same

? Mutation was not published at the time of writing

DNA Testing Laboratory	**Address**	Notes
Antagene	www.antagene.com	Antagene processes blood samples for Optigen tests submitted in Europe
CatDNAtest.org	CatDNAtest.org	
Animal Health Trust (AHT)	www.aht.org.uk	
Laboklin	www.laboklin.co.uk	
Optigen	www.optigen.com	
University of Davis (UCDavis) VGL	www.vgl.ucdavis.edu/services	
vetGen	www.vetgen.com	
University of Missouri (MU)	www.caninegeneticdiseases.net	
Michigan State University (MSU)	eyeresearch@cvm.msu.edu	
Norwegian School of Veterinary Science (NSVS)	Division of Genetics, NSVS, Oslo, Norway	