* Collie Eye Anomaly / Choroidal Hypoplasia (CEA) Test

www.optigen.com

For: Australian Shepherd, Border Collie, Lancashire Heeler, Rough Collie, Shetland Sheepdog and Smooth Collie

Collies share Collie Eye Anomaly (CEA) with several other breeds – it's not just a problem for collies. CEA is more technically known as Choroidal Hypoplasia (CH). It is a recessively inherited eye disorder that causes abnormal development of the choroid - an important layer of tissue under the retina of the eye. This disease is seen most frequently in U.S. collies, but also worldwide in Rough and Smooth Collies, Border Collies, Australian Shepherds, Lancashire Heelers, and Shetland Sheepdogs. Since the choroid layer does not develop normally from the start, the primary abnormality can be diagnosed at a very young age. Regrettably, there is no treatment or cure for CEA.

The symptoms and signs – the clinical phenotype – can vary greatly among affected dogs within one breed, between parent and offspring and even within a litter. This creates a difficult situation for the breeder. Learning about the genetic cause and the course of the disease will help you understand how to manage it better and eventually avoid it altogether with genetic testing.

The primary problem is choroidal hypoplasia (CH). There is under-development (hypoplasia) of the eye tissue layer called the choroid. The choroid appears pale and thin, almost transparent, and the blood vessels of the choroid can easily be recognized in those "thin" areas. The ophthalmologist, looking at the back of the eye (the fundus) with an ophthalmoscope, typically will see an area of choroidal thinning that appears like a "window" to the underlying vessels and sclera.

MILD disease: Mild disease is very common in U.S. collies and is present in the other breeds named above. It is easily recognizable on careful ophthalmologic examination as early as 5 to 8 weeks of age. The lesion appears as an area lateral (temporal) to the optic disc with reduction or absence of pigment so that the underlying vessels of the choroid are seen. The choroidal vessels may be reduced in number and of abnormal shape. The underlying white

sclera might also be visible. Once the retina changes to its adult color around 3 months of age, the normal pigment sometimes masks the changes in the choroid (so-called “go normal” – read more below). In mildly affected dogs, choroidal thinning is the only detectable abnormality and the dog retains normal vision throughout life. However, dogs with mild disease can produce severely affected offspring.

(The eye anomaly “merle” can be confused with choroidal hypoplasia, primarily in dogs from merle to merle breeding and whose coat color is whiter than their littermates. Although both conditions are inherited, can occur in the same breed and exhibit a range of fundus anomalies, there are sufficient dissimilarities for the ophthalmologist to make the distinction.)

SEVERE disease: In severely affected dogs, approximately 25% of dogs with CEA/CH, there are related problems with the health of the eye that can result in serious vision loss in some cases. Colobomas are seen at and near the optic nerve head as outpouchings or “pits” in the eye tissue layers. Colobomas can lead to secondary complications such as partial or complete retinal detachments and/or growth of new but abnormal blood vessels with hemorrhage – bleeding inside the eye. This happens in 5-10% of dogs with CEA/CH, generally by 2 years of age, and can affect either one or both eyes. Complications of severe disease can lead to vision loss, although this disorder only rarely threatens total blindness.

CEA/CH is not progressive in the usual sense. The essential features, choroidal hypoplasia and coloboma, are congenital – the abnormalities develop as the eye develops. These features are also stationary once ocular development is complete around 8-12 weeks of life. Retinal detachments and/or aberrant vessel formation can be congenital or develop later, in general only in eyes with colobomas.

Based on research done jointly by scientists at Cornell University and at The Fred Hutchinson Cancer Research Center, BOTH the mild and severe forms of CEA/CH disease now are proven to result from the exact same gene and mutation in ALL of the affected breeds named above. This disease gene is located on canine chromosome number 37 and the disease-causing mutation has been identified. The mutation acts like a RECESSIVE mutation. That means, both parents of an affected dog must have at least one copy of the mutation and both parents must have passed a copy of the mutation to the offspring. The affected dog is HOMOZYGOUS RECESSIVE – that is, both copies of the gene are mutant. ALL dogs that are homozygous recessive affected will show at least the mild form of the disease. ALL affected dogs, regardless of the actual severity of the lesions, are homozygous for the same mutant gene.

(A dog with one mutant copy and one normal copy of the CEA/CH gene is a carrier – is heterozygous. A dog with two copies of the normal CEA/CH gene is homozygous normal.)

The frequency of CEA/CH disease varies among breeds and by country of origin. The U.S. registration organization, CERF, reported the incidence in the U.S. of choroidal hypoplasia, optic disc/nerve coloboma and retinal detachment among several affected breeds over the period of 1991 to 1999. (Comparable data from other countries isn't available to us yet.)

Frequencies Based on CERF Eye Exams in the U.S. from 1991 to 1999			
	Choroidal Hypoplasia	Coloboma	Retinal Detachment
Collie - Rough & Smooth	66.7%	8.75%	1.88%
Border Collie	2.12%	0.57%	0.06%
Shetland Sheepdog	0.39%	0.79%	0.05%
Australian Shepherd	0.22%	0.27%	0.13%

The frequency of the CEA/CH gene mutation in U.S. Rough and Smooth Collies appears to be extremely high. In general, the frequency of affecteds in Rough and Smooth Collies is well over 50%, and in some populations has been observed to be as high as 85-90% of dogs examined. Of the remaining, most are carriers. The frequency of the CEA/CH gene mutation in European Shetland Sheepdogs appears to be significantly higher than in the U.S.

The OptiGen genetic test for CEA/CH provides a powerful management tool for the breeder. This genetic test can distinguish all three genetic states – normal, carrier and affected. With this information, the breeder can plan matings that avoid producing any affected dogs by always selecting one parent that is normal. The other parent can be normal, carrier or even affected, and no affected dogs will result. (See table at the end.) This breeding recommendation is a big step forward, especially for breeds and countries where frequency of CEA/CH is much lower. Earlier advice cautioned against breeding affected dogs, their parents, their offspring or their siblings (unless eye exams before 3 months of age demonstrate the sib is unaffected).

Understandably, genetic testing will be a difficult tool to use for some breeders of "standard" collies (i.e., Rough, Smooth, Show, Standard) where the disease is very common. In some circumstances, genetically normal – homozygous normal – collies could be difficult to find and it may not be practical for the breeder to plan matings that include one normal dog. And, it may not be reasonable to expect complete avoidance of CEA/CH in one generation. All the same, genetic testing is a sure-fire tool to move toward elimination of the disease. To start, breeding a carrier to a carrier will produce an average of 25% normals, 50% carriers and 25% affecteds. With genetic testing at each subsequent generation, and with a goal of breeding normal by carrier or normal by affected, the

frequency of disease will drop and frequency of normals will increase without loss of other desirable traits valued in collies.

Breeders should pay attention to protecting the genetic diversity of breeds that have very high frequencies of an inherited disease. In the case of CEA/CH, the genetic test can be viewed as an adjunct to traditional strategies for avoiding severe cases of CEA. Over the last 30 years, many animals have been examined and those with only mild CEA (no colobomas or detachments) have been selected for breeding. The result is the percentage of collies affected with choroidal hypoplasia remains high, but the severe grades of the disease (colobomas and retinal detachments) have decreased due to this conscientious breeding.

Even though the ideal recommendation is to breed genetically normals, preservation of other desirable physical traits might override the ideal in the short-term. Reduction or even elimination of the CEA/CH mutant gene can be viewed as a longer-term goal. You should consult with your breed club for further breeding recommendations.

You might ask: if the mild form and the severe form of CEA/CH disease are caused by the exact same genetic mutation, why do some dogs have only mild disease while others have severe disease? Is the severity due to diet, activity, or other insults like infections or trauma? So far, there are no clues that non-genetic factors are responsible. Instead, there are probably other independently acting “modifier” genes that influence CEA/CH gene expression. If that is so, eventually these modifier genes will be detected, although the chore will be difficult. Possibly, by choosing mildly affected dogs and avoiding severely affecteds in a breeding program, breeders have concentrated positive influencing independent modifier genes in their line. The CEA/CH gene frequency may not have changed, but the disease may be partially suppressed as long as the modifying genes are carried along. This is a risky approach, since the identity of those influencing genes – indeed even their number and action – is a complete unknown.

You might also ask: is it true that early choroidal hypoplasia can “go normal,” that is, reverse to a normal appearance? There are occasional reports of puppies, found to be affected as early as 5 weeks of age, that appear to “go normal” when re-examined some months later. The abnormal features seem to disappear or lessen due to pigment changes and masking of the thin choroid areas. (However, if a dog had a coloboma, this will remain – it is a permanent lesion.) The majority of dogs that “go normal” are homozygous for the CEA/CH mutation, especially if they “go normal” slowly or incompletely. A small minority, however, are heterozygous carriers that tend to “go normal” at a very young age. Regardless, the genetic status of such dogs was and remains constant during their lifetime, so these dogs can pass the mutant disease gene to their offspring. Testing will help you identify the genetic status of dogs that have an ambiguous clinical diagnosis.

The CEA/CH genetic test provides the life-long genetic status of a dog for this disease. In conjunction with genetic testing, an eye exam by a veterinary ophthalmologist is recommended before 8-9 weeks of age, with annual eye exams thereafter. The eye exam will give you information about mild versus severe CEA/CH disease among affected dogs. Annual eye exams are always recommended for all dogs of all breeds. Clinical exams detect a wide variety of eye problems, both genetic and non-genetic.

Expected Results of Breeding Strategies for Inherited Recessive Diseases

Parent 1 Genotype	Parent 2 Genotype		
	Normal	Carrier	Affected
Normal	All = Normal	1/2 = Normal 1/2 = Carriers	All = Carriers
Carrier	1/2 = Normal 1/2 = Carriers	1/4 = Normal 1/2 = Carriers 1/4 = Affected	1/2 = Carriers 1/2 = Affected
Affected	All = Carriers	1/2 = Carriers 1/2 = Affected	All = Affected

The table shows the desirable breedings (gray-shaded boxes) which have at least one parent that is Normal by the OptiGen CEA/CH test. All other breedings are at risk of producing pups affected with CEA/CH.

Limits to All Genetic Testing

There are basic limits for any and all DNA genetic tests. Whether a test is mutation-based or marker-based, it identifies only the specific mutation being tested or the association between a specific marker set and the disease. For example, a mutation test detects one specific mutation in one specific gene. If there are several different mutations or several different genes that can cause the same condition, one must discover and then test for each mutation and each gene. Likewise, a marker test uses one marker or set of markers to define a specific condition. If the condition is associated with several different marker combinations, one must discover and then test for each marker combination. It can be difficult or even impossible to know how many mutations or how many marker sets exist in all the members of a specific breed. As more and more dogs are tested, previously unknown variations may come to light.

In the case of CEA/CH, the OptiGen genetic test for the listed breeds is a mutation-based test.

Resources for this article: Acland, G., Retinal Disorders in Border Collies. http://www.sheepdog.com/genetics/eyes.html.
Acland, G., Aguirre, G., Personal Communications.
A.C.V.O. Genetics Committee, "Ocular Disorders Presumed to be Inherited in Purebred Dogs." 1999 Edition.
Riis, R., "Inherited Eye Anomalies of Australian Shepherds, Collies, and Shetland Sheepdogs." In: Small Animal Ophthalmology Secrets, Chapter 38, Hanley & Belfus, Inc., 2002.
Lowe JK, Kukekova AV, Kirkness EF, Langlois MC, Aguirre GD, Acland GM, Ostrander EA. Linkage Mapping of the Primary Disease Locus for Collie Eye Anomaly. Genomics 2003 Jul;82(1):86-95.

How you can participate

The CEA/CH test is done on a small sample of blood obtained by your veterinarian. This allows the lowest risk of contamination of the sample and added assurance of a match of the sample with the identified dog.

*** This is a reprint of the article located on the Optigen website:**
http://www.optigen.com/opt9_test_cea_ch.html

The date of this reprint is 5/18/06. You may wish to go the site to make sure that the information has not been updated.

5 Grades of an affected CEA dog are:

Grade 1	Torturous retinal vessels, extremely small areas of choroidal hypoplasia
Grade 2	Torturous retinal vessels, substantial areas of choroidal hypoplasia
Grade 3	Tortuous retinal vessels, substantial areas of choroidal hypoplasia (blood vessel loss) with pits (colobomas) or areas of out pouching (ectasia) in the posterior segment
Grade 4	All the above defects with a retinal detachment
Grade 5	All the above defects with a retinal hemorrhage
