Known Genetic Diseases Found in Border Collies

To be considered a genetic disease, a health problem needs to have been demonstrated to be heritable, that is, passed on through one or both parents. Some diseases have high heritability, which means if the genes are present, the individual will have the disease, and some diseases have low heritability, meaning both genetic and environmental factors are involved in whether the disease occurs. It is generally easier to control diseases with high heritability because all individuals with the genetic makeup for the disease can usually be identified. The term heritable disease should be distinguished from the term congenital disease, or problems that are present from birth, which may or may not be heritable.

Border Collies are considered to be a generally healthy breed. However, as in all animals, there are some potential health problems. This information is presented to help both breeders and buyers to become more aware of some of the health and genetic issues in the breed at this time.

Disease Summary

The table below summarizes the genetically linked diseases that could be present in Border Collies. This list was compiled from available scientific studies which included Border Collies regardless of subpopulation, since published studies rarely identify subpopulations within a breed (show, agility, pet, working, etc). The list includes diseases which are known to be more prevalent in other subpopulations of Border Collies (i.e. show dogs from other countries) but may still be present at some unknown very low rate in working Border Collies. Listed are upper estimates of incidence rates within our gene pool along with published inheritance modes for these diseases. Available clinical tests to identify affected dogs and genetic tests to identify carriers and affected dogs are also listed.

Summary: Genetically linked diseases that could be present in Border Collies

Disease	Estimated Incidence Rate (a)	Inheritance	Clinical Test	Genetic Test
Collie Eye Anomaly (CEA)	<2.5%	Recessive	Ophthalmological exam (b)	Optigen, Paw Print Genetics, Animal Genetic
Hip Dysplasia	<11% (c)	Complex	Radiographic: OFA, Cornell	None

Disease	Estimated Incidence Rate (a)	Inheritance	Clinical Test	Genetic Test
Epilepsy	<5% (d)	Complex	Physical and neurological exam	None
Early Onset Adult Deafness (EOD)	Unknown	Recessive (e)	BAER test	None
Exercise-Induced Border Collie Collapse (BCC)	Unknown	Complex	None, diagnosis by exclusion	None
Imerslund-Gräsbeck Syndrome (IGS)	Rare (<0.5%) (f)	Recessive	Physical exam and bloodwork	UCDavis, Animal Genetics, Paw Print Genetics
Trapped Neutrophil Syndrome (TNS)	Rare (<0.5%) (f)	Recessive	Bone marrow biopsy	Optigen, Animal Genetics, Paw Print Genetics
Neuronal Ceroid Lipofuscinosis (NCL)	Rare (<0.5%) (f)	Recessive	Physical and MRI exams	Optigen, Paw Print Genetics, Animal Genetics
Multi-Drug Resistance Gene (MDR1)	Rare (<0.5%) (f)	Recessive	None	Vet Clinical Pharmacology Lab at WA State U, Paw Print Genetics, Animal Genetics

a. Estimated incidence rates are for affected dogs, carrier rates will be higher

b. Exams are recommended before 12 weeks of age
c. Hip dysplasia rates are from OFA data for all Border Collies (any registry) where radiographs were submitted from 1974 to 2014
d. There are no published reports for incidence in Border Collies; incidence rates for breeds have been reported to range from 0.5% to 5% with Border Collies having one of the higher incidence rates
e. Genetic studies by Dr Mark Neff suggest (not proven) recessive inheritance
f. Based upon published study from Border Collies without distinction of registry or country

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Hip Dysplasia (HD or CHD)

HD is by far the most prevalent known genetic disease that affects Border Collies. Factors that contribute to the development of HD ultimately cause the hip joint, which is normal at birth, to be damaged. Joint damage called osteoarthritis, also known as degenerative joint disease (DJD) results in response to stresses and inflammatory processes in the joint, usually causing lameness and pain. DJD is, in effect, the identifiable result of factors that cause HD. The standard for diagnosing HD at this time is still the front extended-leg view of the hips on x-ray such as that evaluated by The Orthopedic Foundation for Animals (www.ofa.org). OFA reports an affected rate of 10.8% for Border Collies evaluated from 1974-2015. For those born 2011-2015, the dysplastic rate is 8.4%. This HD incidence ranks them somewhere in the middle of the dog breeds, but may significantly understate the incidence, because X-rays that clearly show HD may not be submitted for evaluation. Other radiological methods of testing for hip dysplasia include PennHIP (www.pennhip.org), which tests for laxity in the hip joint when distraction pressure is applied, and the Dorsolateral Subluxation method, pioneered at Cornell University, where films are taken with the dog in a weight-bearing (kneeling) position.

Data from numerous scientific studies provide overwhelming evidence that HD is an inherited disease. It is not caused by a single gene, however. Rather, it is polygenic — caused by a number of primary genes interacting with one another. The number of genes involved, combined with the high incidence, means it's probable that most Border Collies are at least carriers of one or more of the genes that can contribute to the development of HD, even if they don't have the disease themselves. To confuse matters more, the expression of the disease is affected by environmental conditions such as the type and amount of food a dog gets at critical growth stages, as well as the type and amount of exercise and activity it gets. It must be remembered, however, that these environmental factors do not cause HD. They merely affect whether the HD genes present in that individual will be expressed to the fullest. Even if the expression of HD in a certain individual is suppressed by careful control of environmental factors, you have not changed the dog's genetic makeup. That dog will still pass on the genetic tendency for HD just as if it actually had the disease. Conversely, if a dog does not have the genes for HD, it won't develop the disease no matter how it's raised.

Some estimates that HD may occur in one out of four dogs may seem falsely high if the presence of HD is defined by dogs showing significant lameness. The clinical symptoms of HD do not always correlate well with the severity of the disease as judged by radiological findings. Border Collies with HD that are fortunate enough to show few if any symptoms may have progeny that are not so fortunate. The exact complex combination of genetic and environmental factors that contributed to an individual's lack of symptoms will not occur in its pups. Therefore, it is important to remember that a high tolerance of an individual dog for the effects of HD does not mean that individual is suitable as a breeding prospect.

Because the disease is polygenic, no genetic test for it has yet been developed. The best way, at this time, to avoid producing puppies with a predisposition to develop HD is to x-ray both parents before breeding, and be aware of the hip status of other related dogs such as the parents' other progeny, the parents' parents, and the littermates and half siblings of the parents. The more tested, unaffected dogs there are in the pedigrees, the better the chances of producing unaffected pups. Unfortunately, even following the most stringent guidelines, puppies may still be produced that will develop HD. This does not mean there's no point in testing parents before breeding them. This line of false reasoning is akin to arguing that, because working parents will occasionally produce pups that won't work, there's no point in testing the working ability of breeding stock. Selection for good hips will increase your chances of producing pups with good hips, but it's unrealistic to expect that puppies with HD will never be produced from tested, unaffected parents. Likewise, it is unrealistic to expect every dog who has ever produced a pup with HD to be banned from breeding. Since it's likely that most non HD-affected Border Collies are carriers of one or more of the genes for HD, most dogs will produce at least one pup with HD if bred enough times. Sooner or later, a cross with another carrier will produce the wrong combination of the HD genes and an affected pup will result.

Given the incidence and complexities involved with HD in our breed, our recommendations at this time are to breed only hip tested, unaffected parents. Also, try to plan crosses having as many tested, unaffected dogs in the pedigrees of both parents as possible. If an affected puppy is produced from a cross of two unaffected parents, at the very least, don't repeat that particular cross because that affected puppy has proven that the two parents can together provide the right combinations of genes to create more puppies with HD.

References for HD:
Quantitative evaluation of hip joint laxity in 22 Border Collies using computed tomography, J Vet Med Sci, 2009 Feb:7192):247-50; abstract at http://www.ncbi.nlm.nih.gov/pubmed/19262043

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Epilepsy

Epilepsy is a disease characterized by seizures, or “fits” as they are sometimes called. Although Border Collies, like all other breeds, can be affected with epilepsy, the incidence and heritability in our breed are unknown.

Since there can be many causes, determining why a dog has seizures is a complex process. The diagnosis of primary or idiopathic epilepsy is made based on negative results for other causes of seizures. Therefore, it is a diagnosis made by exclusion rather than by a specific test. ABCA is supporting research aimed at finding the genes that may cause epilepsy in the breed, but so far even the most cutting edge research methods have proved unsuccessful. The most recent work sponsored by the ABCA was a genome-wide association study conducted in 2013, using DNA samples from 103 epileptic dogs and 105 control dogs, which failed to detect any chromosomal regions associated with idiopathic epilepsy. The findings, as summarized by the Principal Investigator, Dr. Mark Neff: “Although the outcome . . . does not exclude a genetic influence on epilepsy in the working Border Collie breed, the result does suggest that any individual genetic factors present are of relatively small effect. This has a practical implication — that selective breeding is unlikely to reduce the incidence of epilepsy in the breed.”

Since we have little breed-specific information to go on, our breeding recommendations concerning this disease are based on those for other affected breeds in which the disease is more well-defined. Recommendations are: Do not breed affected dogs. If two unaffected dogs produce an affected puppy, do not repeat that cross.

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Collie Eye Anomaly (CEA)

CEA is a congenital disorder where the parts of the eye, particularly the retinal area, do not develop normally. The severity of the disease ranges from no visual impairment to blindness. It is not a progressive disease and affected dogs usually have only mildly impaired vision.

CEA is an autosomal recessive disorder. Autosomal means it is passed on and expressed equally in males or females. Recessive means a dog may carry a mutated CEA allele (one form of a gene that has various forms) and pass it on to its offspring without having the disease itself. A dog is defined as Clear (or Normal) if it has no alleles carrying the CEA mutation. A dog is defined as a Carrier if it has one mutated allele and one normal allele. The eyes of both the Carrier and the Clear dogs will be unaffected by the disease. A dog which has two mutated alleles is defined as Affected. The outcomes of the different crosses of these dogs are as follows:

- Clear X Clear = 100% CEA Clear puppies
- Clear X Carrier = on average, 50% Clear, 50% Carriers
- Clear X Affected = 100% Carriers
- Carrier X Carrier = on average, 25% Clear, 50% Carriers, 25% Affected
- Carrier X Affected = on average, 50% Affected, 50% Carriers
- Affected X Affected = 100% Affected

It is possible to determine whether a dog is Affected with CEA by having it examined by a Diplomate of the American College of Veterinary Ophthalmologists (DACVO). To be sure of obtaining accurate results, however, puppies should be examined before they are 9 weeks of age, because some Affected dogs have a mild form of the disease called "go normal," where normal tissue grows over and covers up the diseased area of the eye as the dog matures. These "go normal" dogs cannot reliably be identified by an eye exam in adulthood, but they will always pass on a CEA gene to their offspring just as if they had full blown expression of the disease.

Since an ophthalmic exam cannot distinguish between Carrier dogs and Clear dogs, at one time the only way to know if a dog was a Carrier was for it to produce an Affected puppy. Since there were so many unknown Carriers, that meant there was no way to keep from inadvertantly producing Affected pups. Since 2005, however, there has been a reliable DNA test for the CEA mutation, which can determine whether a dog is Affected, a Carrier, or Clear. That test was developed by Dr. Gregory Acland, with cooperation and support from the ABCA. Some of the companies that offer DNA tests for the CEA mutation, and their prices as of July 2016, are:

- OptiGen (www.optigen.com), $180 (25% discounts available)
- Paw Print Genetics (www.pawprintgenetics.com), $80
- Gene Check (www.genecheck.com), $55

It is recommended that breeders utilize the DNA test to determine the status of all dogs used for breeding. A Clear (Normal) dog bred to a Clear (Normal) dog will produce only Clear puppies, so the offspring of such a mating need not be DNA tested; their status is known. An Affected dog should be bred only to a Clear dog, and only when the dog has exceptional merits which would justify a breeding that will produce pups who will all be Carriers. Carriers, too, should be bred only to Clear dogs, in order to avoid producing Affected pups; at the same time, breeders should not exclude Carriers from their breeding program, as this would be detrimental to the goal of maintaining the highest level of working ability in our breed and would also tend to constrict the gene pool. All pups with a Carrier parent should be tested to determine their CEA status before being bred. If testing all breeding stock is not feasible, at a minimum breeders should ensure that one parent of any litter is DNA Clear, as this is the only way to be sure that Affected pups will not be produced. Breeders and owners should be frank and forthcoming in informing anyone inquiring about a breeding or a puppy purchase about the CEA status of the dogs involved, and the significance of that for any offspring they may have.

References for CEA:
Collie Eye Anomaly Genetics, http://www.optigen.com/opt9_gregmess.html
*Collie Eye Anomaly/Choroidal Hypoplasia (CEA),*http://www.optigen.com/opt9_test_cea_ch.html

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Early Adult Onset Deafness (EAOD or EOD)

EAOD is one of three types of heritable deafness that can be found in border collies — the other two are congenital sensorineural deafness (which occurs in pups by the time they are 8-10 weeks old), and old-age deafness. EAOD typically strikes dogs in their prime, between the ages of two and six years old. It can occur even later, up to age 8, but at that point it cannot be reliably distinguished from old-age deafness at our present state of knowledge.

EAOD was first described in the paper linked below. ABCA was actively involved in the research leading to that paper, and in the collection of samples used in that research both before and after publication of the paper. Two of the authors, Drs. Mark Neff and Alison Ruhe, have continued research into the disease, and have narrowed their search for the causative mutation to five variants in a region of chromosome 6. They are currently offering a marker test for the disease through projectDOG (fidelis.projectdog.org) at a cost of $145 (other DNA tests can be obtained at no additional cost), but this test is expected to be offered only through September 30, 2016. Another of the authors, Dr. Hannes Lohi, has continued research into this form of deafness at the University of Helsinki, drawing on samples from many different countries.

The incidence rate for EAOD in the Border Collie breed is unknown at this time, but because several high-quality working dogs in the US were sought-after sires before they were found to have produced affected pups, the incidence is almost certainly increasing in North America.

References for EAOD:
Variation in Genes Related to Cochlear Biology is Strongly Associated with Adult-Onset Deafness in Border Collies, 2012, http://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1002898

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Exercise-Induced Border Collie Collapse (BCC)

Usually referred to as Border Collie Collapse or BCC, this disorder refers to a condition seen in some Border Collies during or after intense exercise. Seldom do dogs actually collapse during an episode, but they stagger or wander aimlessly, often with an impaired gait in which the toes can knuckle under, with the top of the foot scuffing the ground. They also appear dazed and disoriented. Episodes last a fairly short time, with full recovery usually within 20-30 minutes. They can come on while the dog is exercising, but also can occur up to 10 minutes or so after exercise has ended.

Although exercise in high heat and humidity is more likely to bring on an episode, BCC is not the same as hyperthermia or heat stroke. Body temperatures can be extremely high during an episode, but they are not higher than those of normal exercise-tolerant border collies performing the same exercise.

Research suggests that BCC is an episodic diffuse or multifocal central nervous system disorder. Pedigree analysis suggests that BCC is inherited, but mode of inheritance has not been determined.

References for BCC:
Evaluation of Dogs with Border Collie Collapse, Including Response to Two Standardized Strenuous Exercise Protocols, JAAHA, vol. 52:5 (Sep-Oct 2016)
https://www.aaha.org/public_documents/professional/resources/jaaha_52.5_border_collie_collapse_part_1.pdf
Border Collie Collapse: Owner Survey Results and Veterinary Description of Videotaped Episodes, J Am Anim Hosp Assoc, vol 52:6 (Nov-Dec 2016)
https://www.aaha.org/public_documents/professional/resources/jaaha_52.6_border_collie_collapse_part_2.pdf

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Cobalamin Malabsorption Syndrome

Cobalamin Malabsorption Syndrome, often called IGS, after its human version, **Imerslund-Grasbeck Syndrome**, is a hereditary disease that can be found in Border Collies. It results in a serious Vitamin B12 (cobalamin) deficiency, because the dog's intestine is unable to absorb that vitamin. Symptoms include lethargy and lack of appetite, but the most noticeable symptoms are usually persistent diarrhea and nausea or vomiting. They appear in puppyhood, usually before the age of six months, but the condition has often not been accurately diagnosed until much later. Once the correct diagnosis has been made, symptoms are relieved by regular subcutaneous injections of cobalamin, which dog owners can learn to give at home.

The pattern of inheritance is autosomal recessive, like CEA. This means that two dogs who do not themselves have the disease can produce pups who do, if both of them are carriers. Fortunately, there is now a DNA test for the disease, which can determine whether a dog is Normal, a Carrier, or Affected. It can be used in making breeding decisions, as well as in diagnosing a dog suspected of having the disease. A number of companies offer tests for this condition under various names; their prices as of July 2016 are:

- OptiGen (www.optigen.com), $95; "I-GS"
- Paw Print Genetics (www.pawprintgenetics.com); $80; "Intestinal cobalamin malabsorption (Border Collie type)"
- Veterinary Genetics Services (vetgen.com); $65; "Cobalamin (B12) malabsorption"
- Veterinary Genetics Laboratory (www.vgl.ucdavis.edu/); $50; "IGS"
- Animal Genetics (animalgenetics.com); $45; "IGS"

Discounts from these prices are often available if more than 1 test is being purchased, if the dog has previously been tested for something else, etc.

Two studies (one in the US and one in Europe) have shown that the prevalence of carriers in the Border Collie populations studied was 6%, which indicates that 0.1% of Border Collies would likely be affected. Of course, a popular sire who carries or is affected by the disease and who has many offspring could result in raising the incidence of the disease in our population.

It is recommended that the DNA test be administered prior to breeding when there is any reason to believe that the disease may be present in the sire's or dam's lines. Affected dogs should not be bred, and Carriers should only be bred to dogs who have tested Clear. Breeders can be certain they will not produce pups afflicted with this disease if one parent has been tested and found to be Clear.

References for IGS:
A Frameshift Mutation in the Cubilin Gene (CUBN) in Border Collies with Imerslund-Grasbeck Syndrome (Selective Cobalamin Malabsorption), http://journals.plos…144#authcontrib
Imerslund-Grasbeck Syndrome (IGS) or intestinal malabsorption of cobalamin in Border Collies, http://www.genomia.cz/en/test/igs/

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Trapped Neutrophil Syndrome (TNS)

TNS is a disease in which proto white blood cells (neutrophils) are produced but are not able to move from the bone marrow into the blood stream. As a result, the affected dog has a compromised immune system and is not able to fight off infection. Pups usually succumb to infections of various kinds or are euthanized — usually within their first few months of life, although very rarely they may survive into their second or even third year.

The disease is caused by a deletion mutation in the VPS13B gene, and has an autosomal recessive mode of inheritance, so a dog will not inherit the disease unless both parents are carriers of the mutation (affected dogs rarely if ever survive long enough to reproduce). The disease was discovered in Australia, and the incidence (at least in North American border collies without Australian/New Zealand ancestry) appears to be very low, although some cases resulting in death in early puppyhood may go undiagnosed.

It is recommended that the DNA test be administered prior to breeding when there is any reason to believe that the disease may be present in the sire's or dam's lines. Affected dogs should not be bred, and carriers should only be bred to dogs who have tested clear.

Some of those offering genetic tests for TNS, and their prices as of July 2016, are:

- OptiGen (optigen.com) $95 (discounts available)
- Veterinary Genetics Lab (www.vgl.ucdavis.edu) $50 (discounts available)
- Paw Print Genetics (www.pawprintgenetics.com) $80 (discounts available)

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ABCB1 (also known as MDR1)

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ABCB1 is a gene which has a **multi-drug sensitivity** allele. It has an autosomal recessive mode of inheritance. A dog that has two copies of the mutated allele will be sensitive to a number of frequently used drugs, including ivermectin. A dog who has one copy of the mutated allele is a carrier: it will not display drug sensitivity, but can pass on the mutation to its offspring. These mutations are present in several herding breeds, particularly the Collie, Australian Shepherd and Shetland Sheepdog, as well as some non-herding breeds, e.g., the Silken Windhound. It has been found in Border Collies, but very rarely

The first reference below describes the workings of the gene and the effects of the mutation. It finds that even dogs affected with the mutation do not have toxic reactions to recommended dosage levels of ivermectin and related drugs for heart worm prevention, but can have serious reactions to larger doses (often administered from formulations intended for large animals). It estimates that about 1% of Border Collies carry either one or two copies of the mutation.

The second reference describes a different mutation that was found in a single Border Collie in China.

References for MDR1

Toxicology of Avermectins and Milbemycins (Macrocylic Lactones) and the Role of P-Glycoprotein in Dogs and Cats, Vet Clin North Am Small Anim Pract., 2012 Mar; 42(2):313-vii. www.ncbi.nlm.nih.gov/pmc/articles/PMC4152460/

Novel insertion mutation of ABCB1 gene in an ivermectin-sensitive Border Collie, J Vet Sci. 2010 Dec; 11(4): 341-344. www.ncbi.nim.nih.gov/pmc/articles/PMC2998746/