Understanding the Multi-Drug Resistant Gene Mutation in Border Collies

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Have you heard of dogs having a "bad reaction" to Ivermectin or certain other drugs? This can be caused by drug interactions, but it's often caused by a mutation to the multi-drug resistance-1 (MDR1) gene. This mutation is called MDR1-1Δ, and in this article we want to lay out some important information you should know about it.

The MDR1 gene (also sometimes referred to as the ABCB1 gene) produces a protein that protects the brain from certain drugs and also aids inclearing these drugs from the body through organs such as the liver and kidneys. These include some drugs used to treat cancer, infections, pain, parasites, pre-anesthetic drugs and anti-diarrheal medication. Aside from the over-the-counter anti-diarrheal drug loperamide (Imodium), most of these drugs require a prescription.

TheMDR1-1Δ mutation interferes with this important protective function. Like most single gene mutations, a dog can have one mutated MDR1 gene and one normal gene (heterozygote) or two mutated genes (homozygote). One copy of the gene is contributed by each parent. A dog that carries two copies of the mutation will not produce any of the protective protein, and it will pass one copy of the mutated gene to all of its offspring. A dog that carries one copy of the mutation will pass on a copy of the mutation to roughly half of its offspring. But in one very important respect, the dog that carries a single copy of the mutated MDR1 gene is different from the"carrier" dogs who are heterozygous for other most commonly known mutations, such as CEA, where a heterozygote is an unaffected carrier.**The dog who is heterozygous for the MDR1-1Δ mutation may display symptoms of the disorder.** Because each of the two genes separately produces the MDR1protein, its normal gene will produce the protective protein, but the mutant gene will not. Depending on other regulating factors present in the body at the time, a “carrier” of the MDR1 gene mutation has the potential to produce only half or less of the normal MDR1 protein needed to protect its brain from certain drugs. As a result, these heterozygous dogs range from essentially normal to mildly affected to significantly affected, with the most being mildly affected.

Of the drugs causing neurotoxicity in dogs due to the MDR1-1Δmutation, the avermectin class, which includes Ivermectin, has the most potential for toxicity. However, even dogs with the MDR1 mutation should be able to tolerate the low doses of avermectins in each of the commercial heartworm prevention preparations. For example, Heartgard contains 6 to 12mcg/kg of Ivermectin. In dogs having the MDR1-1Δ mutation, no toxicity was seen when these dogs were given 28 to 35.5 mcg/kg monthly for one year, so the safety margin should be wide enough in heartworm-only heartworm medicines. By comparison, dogs without the mutation should be able to tolerate oral dosages as high as 2,500 mcg/kg. However, if the concentration is high enough, all dogs will show neurotoxicity to Ivermectin. For more general information on the MDR1 mutation and gene test in dogs, go to: https://vcpl.vetmed.wsu.edu

A gene test for the MDR1-1Δ mutation became available for dogs around 2004. While many collies and collie type breeds have been shown to have a high frequency of the mutation, until the last few years no cases of confirmed purebred border collies had been found that were either heterozygous or homozygous for the MDR1-1Δ mutation in the US. Recently, however, there have been some reports of working border collies with the mutation. The mutated MDR1 gene has been reported by DNA testing companies to be at less than1% in the US, so it's fortunately still considered a rare mutation in purebred border collies. Therefore the presence of this mutation in the breed is at a stage where it can be more easily controlled than some mutations that affect a large portion of the gene pool. Most importantly, however, because even the heterozygous, "carrier" state of the MDR1 mutation has the potential to cause health problems from toxicity to drugs the MDR1 protein protects for, there is more concern for controlling the presence of this gene mutation in both the heterozygous and homozygous form. This low incidence in the breed and the fact that even heterozygotes can be affected cause the ABCA's Health & Education Foundationto suggest specific breeding recommendations for these dogs.

The ABCA registry does not prohibit breeding of dogs with genetic problems; however, breeding recommendations are made in some cases. These breeding recommendations are not simple, across-the-board advice but instead take into account such factors as the frequency of the mutation or problem in the breed, the seriousness of the problem, and the mode of inheritance. There is a fine balance between trying to keep a currently low-frequency mutation with potential to affect health even in the heterozygous state from spreading in the breed, and preserving important working lines thatmight have a higher frequency of the mutation than the rest of the gene pool. The goal is to try to strike and maintain a healthy balance.

In the case ofMDR1,if a dog is heterozygous or homozygous for the mutation, the recommendation is not to breed the dog unless it is of the very most superior working ability, with other desirable attributes, and only to cross such a dog with dogs tested clear of the MDR1 mutation and also of very superior working ability. Even if you feel you must breed the dog, limit the number of times a heterozygote or homozygote is bred in order to prevent the rapid spread of the mutant gene throughout the population, such as can happen in the case of a popular sire. Be aware these crosses will produce more potentially affected heterozygotes – an average of 50% heterozygotes in aheterozygote-to-normal cross and 100% heterozygotes in ahomozygote-to-normal cross. Obviously, then, breeding homozygotes is very problematic, in that it will increase the prevalence of heterozygotes in the breed, and all puppy buyers will need to be told that the pups could experience neurotoxicity when given certain drugs. It's advisable that the offspring of the heterozygote x normal crosses be tested to determine which ones are normal and which ones are heterozygotes. If the tested normal offspring are superior working dogs with the other desirable attributes, then the line has been cleared of the MDR1 mutation and, depending on other considerations, such as temperament, physical fitness for work, absence of other health problems, etc., can be safely used for breeding. The heterozygous offspring present a more involved management problem. These puppies should be placed with their new owners with full disclosure of the potential problems a MDR1 heterozygote might encounter. Thenew owners of these heterozygous offspring must be made aware of the importance of following the more stringent breeding guidelinesoutlined here in order to minimize the mutant gene, and heterozygotes sold to non-working homes should be registered with NB (non-breeding) status. Make sure the new owners are awarethis situation is different from the usual carrier-to-clear

breeding for a recessive gene mutation, in that heterozygotes and their heterozygous offspring may well experience symptoms of the disorder. In addition, because the MDR1 mutation is rare in our breed, it's important not to increase the frequency any more than necessary with the goal of preserving important genetics and maintaining a healthy gene pool. Controlling what happens with puppies once they leave the breeder can be very difficult. This is one reasonselection criteria should be more targeted to producing and continuing the line with only MDR1 normal offspring.

There are undoubtedly many potentially harmful mutations in the breed that we don't yet know about and for which there are no DNA tests. This unfortunate truth is merely a fact of life in all living beings. Although we will never be able to rid the breed of allmutations causing disease, we can do our best to minimize and prevent spread throughout the breed of those causing significant harm that we do know about. Breeding recommendations tailored for the specific problems and breedcan help keep the gene pool as healthy as possible.
