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Collies and the *mdr1* deletion gene—setting the record straight

Sharon Vanderlip, D.V.M.

Recently an article was published in a British Collie magazine, *Round Up*, about the *mdr1* gene. The article was erroneous and misleading on many counts. It suggested that the *mdr1* deletion gene was responsible for a plethora of problems in Collies, ranging from organ (liver and kidney) problems, to fading puppy syndrome, to small litter sizes. The article also wrongly stated that Collie eye anomaly (CEA) and hip dysplasia (HD) cannot be "eradicated" from the Collie breed. **I am writing this response to the *Round Up* article because I strongly disagree with it.**

It is troubling when individuals misinterpret information and then spread misinformation. In response to the *Round Up* article, I am

1. addressing the article's incorrect statement about the inability to eliminate CEA and HD in Collies
2. addressing speculations and errors in the article about the *mdr1* gene and the *mdr1* gene deletion
3. providing information and clarification
4. referring readers directly to scientific studies and sources of accurate information, including scientific journals and helpful websites, so readers can access correct, detailed information about the *mdr1* gene in Collies and make informed, educated decisions about their dogs and their breeding programs

In addition, I called Dr. Katrina Mealey at Washington State University College of Veterinary Medicine and sent her the *Round Up* article. Dr. Mealey is the veterinarian who discovered the *mdr1* deletion gene and is a leading researcher and authority on the subject. We share the opinion that the *Round Up* article's premise that the *mdr1* deletion gene was responsible for liver and kidney and reproductive problems in Collies is very wrong.

Dr. Mealey's website: http://www.vetmed.wsu.edu/depts-vcpl/

The *Round Up* article also mentioned cortisol studies to support its claims. Dr. Mealey's publication regarding decreased adrenal function is listed on her website under the research section and I encourage readers to access it so they can obtain the *correct* information regarding this study:

Mealey KL, Gay JM, Martin LG, Waiting DK. Comparison of the hypothalamic-pituitary-adrenal axis in MDR1-1D and MDR1 wildtype dogs. J Vet Emergency Crit Care 2007;17:61-66.

The *Round Up* article mentioned genetically engineered knockout mice (the mice used in research that have the mdr1 gene deletion) and ivermectin sensitivtiy. I refer readers to an *accurate* source for the story and additional references on the National Institutes of Health website:

http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1636591

Dr. Mealey adds that the knockout mice (for the mdr1 gene deletion) "live normal lifespans with no increase in liver or kidney disease and that they reproduce normally."

First, I will state the obvious: Without all of the facts and without accurate information, there is only speculation—simply guessing—and that can be dangerous and counter-productive.

There are innumerable causes of liver, kidney, reproductive, and perinatal diseases. The etiologies are usually quite complicated and often multiple. Sometimes the problems are of an inherited (genetic) nature. To know the true cause of any medical problem, physical examinations and repeated laboratory work must be done, medical records must be carefully maintained, and an accurate diagnosis must be made by a veterinary professional. All of these procedures are costly and often declined by clients for financial reasons, so veterinarians cannot always obtain the information needed. In cases of death, necropsies (animal autopsies) should always be performed. This is something many clients find objectionable for personal reasons, so they often decline the procedure, leaving many cases undiagnosed.

The *Round Up* article incorrectly suggests that the high incidence of fading puppies, reproductive problems, infertility, and poor semen quality in the UK Collies is due to the *mdr1* deletion gene. My veterinary practice focuses on reproductive medicine and I work with numerous clients' Collies yearly (plus my own Collies). I see very few cases of reproductive problems, low fertility, or abnormal semen in Collies. In fact, Collies are less affected with these problems than many other breeds. The problems UK Collies suffer from are likely due to a variety of causes. Because the problems are reportedly so widespread, they may also be of a genetic (inherited) nature. There is no research or data to support the *Round Up* article's premise that these problems are due to the *mdr1* gene deletion. As Dr. Mealey stated in one of our

correspondences, "Since 75 percent of Collies have the *mdr1* mutation, it certainly would seem that fertility is NOT a problem!" I agree. Dr. Mealey added that the genetically engineered knockout mice (mice that have the mdr1 gene deletion) also reproduce normally.

Mention of the high incidence of hip dysplasia in the UK Collies was included in the *Round Up* article. Because of the Collie's anatomy, vertebrate structure, and musculature, HD was previously uncommon in Collies until recent decades and, if one is to believe the *Round Up* article, is a growing problem in UK Collies. HD is uncommon in US Collies, except in a few specific lines. The US Collie is larger than the UK Collie, so one might expect the incidence of HD to be greater in US Collies than in UK Collies, but that is not the case. HD is also found in a few lines of Canadian Collies. We have traced their origins through pedigree analysis. HD appears to be a relatively recent genetic development (in relation to the evolution of the breed) that is more specific to UK Collies.

The *Round Up* article wrongly states HD and CEA cannot be eradicated from the breed. CEA and HD *can most definitely be eliminated* from Collie lines, *while maintaining desirable Collie type and temperament*. This has already been proven. But as long as some breeders continue to knowingly export, import, and breed Collies that have hip dysplasia in their pedigrees, or continue to breed CEA affected to CEA affected Collies, the problems will persist. *It is these unconscionable breeders who continue to propagate problems in the breed.*

One of the oddest incongruities in the *Round Up* article is the statement that *mdr1* (meaning the *mdr1* deletion gene) can be eradicated, but that CEA cannot be eradicated. This is illogical because

1. CEA and *mdr1* deletion gene have about the same prevalence within the breed (about 75 percent)
2. In both CEA and *mdr1* gene deletion cases, the normal allele is dominant.

Thus, the same type of breeding program would be implemented to eliminate each problem, with the same percentage results. Neither condition is easier or more difficult to eliminate.

CEA has the diagnostic advantage in that dogs carrying one or more "normal eyes" genes, or dogs that are homozygous for the CEA gene, can be identified by ophthalmologic examination. (Eye checks must be done at a young age so "go normals" are not confused with true genetic normals). For CEA, as for the *mdr1* gene, a DNA test is required to identify all three allelic states: homozygous normal, heterozygous, and homozygous affected. Without this information, breeders cannot make informed decisions about breeding their animals.

The *Round Up* article incorrectly states that antibiotics kill bacteria because bacteria do not have the *mdr1* gene and thus do not produce P-glycoprotein and then suggests that antibiotics are deadly for Collies for the same (incorrect) reason. The article confuses P-glycoprotein with

peptidoglycan, two completely different substances. The reason antibiotics kill bacteria is because the bacterial cell wall differs from that of other organisms by the presence of peptidoglycan. Some antibiotics inhibit a specific enzyme needed to synthesize the bacterial cell wall. Other antibiotics bind to the cell wall and inhibit peptidoglycan cross-linking, causing bacterial cells to rupture and die. This has nothing to do with the *mdr1* gene or with P-glycoprotein.

At this time, there are no antibiotics currently listed on the dangerous drug list for Collies with the *mdr1* gene deletion. Here is the list:

http://www.vetmed.wsu.edu/depts-VCPL/drugs.aspx

Clearly, the *mdr1* gene and its interactions with P-glycoprotein and substrates is a very complicated subject. A solid understanding of molecular biology, genetics, and pharmacology are helpful to fully appreciate the complexities. This is why it is so important for breeders to obtain their information from accurate, researched, well-documented sources.

The key thing to keep in mind is that the *mdr1* gene deletion *causes problems **when** a Collie that is homozygous for the deletion gene (-/-) is given a drug that is a substrate for P-glycoprotein. This is because that particular drug cannot be transported out of the nervous system because P-glycoprotein is not available to do the job.* Remember also that *not all drugs are P-glycoprotein substrates* and that we have many other pharmaceutical treatment options for Collies.

The *mdr1* gene deletion is widespread in Collies. Studies report approximately 75 percent of the Collie population currently carries the *mdr1* gene deletion. Other studies indicate approximately 30% of Collies are homozygous for the *mdr1* gene deletion and approximately 40% are heterozygous. This means that one quarter to one third of Collies do *not* carry the *mdr1* deletion gene and are homozygous “normal”.

The *mdr1* gene deletion has been found in ten breeds to date. It has also been found in mixed breeds. Through DNA studies, the *mdr1* gene deletion has been determined to date back as far as the 1870s, tracing back to a single animal that lived in England before many breed registries were maintained and before some breeds were developed. Here is the story: http://www.msnbc.msn.com/id/5518665

Here are a couple of relevant scientific publications:

Neff MW, Robertson KR, Wong AK, Safra N, Broman KW, Slatkin M, Mealey KL, Pedersen NC. Breed distribution and history of canine mdr1-1Delta, a pharmacogenetic mutation that marks the emergence of breeds from the collie lineage. Proc Natl Acad Sci U S A. 2004 Aug 10;101(32):11725-30. Epub 2004 Aug 2.

Mealey KL, Munyard KA, Bentjen SA. Frequency of the mutant MDR1 allele associated with multidrug sensitivity in a sample of herding breed dogs living in Australia.
Vet Parasitol. 2005 Aug 10;131(3-4):193-6.

Knowing the high prevalence of the *mdr1* gene deletion in the Collie population allows us to understand and assess the statistics and significance of clinical cases. For example, if we review 100 Collie cases of any given medical problem, we must keep in mind that if approximately 75 percent of the Collie population carries the *mdr1* gene deletion, then approximately 75 percent of Collies with the medical problem will likely also carry the *mdr1* gene deletion. This does not mean the *mdr1* gene is the cause of the disease. It means that the gene is widespread in the population. You could look at this a different way using colors. There are more sable Collies than white Collies. So, for any given medical problem, more sable Collies will be affected with the problem than white Collies. This doesn't mean sable Collies are less healthy than white Collies. It means that there are more sable Collies in the population.

Obviously the *mdr1*gene deletion does not have the devastating effects on the liver and kidneys, or reproduction that the *Round Up* article speculates. If the statements were true, the statistics would support the conclusions. **The incidence of the *mdr1* gene deletion in US Collies is approximately the same as the incidence in UK Collies, to the best of our knowledge at this time. However, the US Collies are overall a hardy and fertile group.** Different lines naturally have different problems, but nothing as widespread and severe as the *Round Up* article and comments suggest the UK Collies are currently experiencing. Again, I question how much of a role genetics may be playing in these problems?

In addition, if the *mdr1* gene deletion created the adverse effects the *Round Up* article suggests, then Collies (and perhaps the other nine breeds that carry the *mdr1* gene deletion) would have likely succumbed to the gene's ill effects long ago and would not have survived 140 years since the 1870s, when the *mdr1* gene deletion is thought to have occurred. Researchers, scientists, and veterinarians would have made the clinical observations, diagnoses, and statistical correlations and published their findings in peer-reviewed scientific journals over the years since the *mdr1* gene deletion was discovered. That is not the case.

Interestingly, the *mdr1* gene deletion might be a beneficial future tool in treating cancers or diseases of the brain. In order to successfully treat some brain cancers and brain diseases, needed drugs must penetrate brain tissues and remain there. Dr. Mealey is investigating ways to exploit the *mdr1* gene deletion so that chemotherapeutic drugs can remain in the brain where they are needed in some cases, instead of being transported out of the brain. She hopes that by finding ways to use the *mdr1* gene deletion her research group can provide "a less toxic, more effective way to treat cancers or diseases of the brain."

Here is the link to Dr. Mealey's *mdr1* gene research and selected publications:

http://www.vetmed.wsu.edu/depts-VCPL/publications.aspx

As a Collie breeder and veterinarian for more than 30 years, I have extensive medical records, pedigrees, necropsy reports, and laboratory values on numerous Collies and Collie lines worldwide. In my veterinary practice I have treated countless Collies and other breeds now known to carry the *mdr1*gene deletion. I routinely run laboratory tests (including liver and kidney function tests and DNA tests for the *mdr1* gene deletion) on my patients, have performed several thousands of major surgeries, and routinely combine anesthesia and antibiotic protocols. In addition, my practice is reproductive medicine and surgery, so I have seen a tremendous number of reproductive (including infertility) cases. **I have not seen anything that supports any of the speculations made in the *Round Up* article.**

In addition, I have owned UK Collies and US Collies. I was among the first to report drug toxicities in Collies in the early 1980s, before these drugs were recognized as potentially dangerous for some animals. **I have owned Collies homozygous and heterozygous for the *mdr1* gene deletion, and I own Collies that are homozygous normal non-carriers of the *mdr1* gene deletion. There have been no major differences in their health, fertility, or lifespan (13 to 16 years), regardless of their *mdr1* status. This correlates with my findings in veterinary practice.**

As responsible, ethical breeders, we strive to eliminate problem genes from our dogs' lines. To do this we must

- DNA test our Collies for all genetics problems for which DNA tests are available
- test and certify for other conditions for which laboratory tests are available (such as thyroid certification)
- share accurate information with one another
- take into consideration all aspects of our breeding program
- give priority to eliminating the most severe problems first
- give serious consideration to the possibility of inherited disorders when we see certain conditions arising with increasing frequency in specific lines
- avoid unfounded speculations and jumping to conclusions

We cannot clear our animals of all problems in one generation, but we *can* eradicate their genetic problems over time with careful, selective breeding programs. It takes time (several years), knowledge, patience, dedication, education, commitment, space, and money. It means that if there is something seriously wrong with a dog, it should not be bred. It also means giving high priority to eliminating the most serious problems first. For example, no ethical breeder would breed a dog with HD or with a history of HD in the dog's close relatives. Producing a dog

that can walk and see normally is much more important than producing a dog that can safely receive a dose of ivermectin.*

I strongly encourage all readers to consult with their veterinarians and veterinary colleges, to read the *scientific* studies and *scientific* literature, to share accurate information, *to make their own decisions based on scientific* information (and not on speculation), and to make wise breeding decisions in the best interest of the breed.

Note: In my new Collie book (anticipated release 2010), I have dedicated an entire chapter to the *mdr1* gene deletion.

*In our veterinary practice we have used milbemycin oxime (Interceptor) once monthly (at the recommended dose by weight) for more than 15 years, and have seen no adverse effects, even in Collies that are homozygous for the *mdr1* gene deletion.

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If you are new to the breed and unfamiliar with the *mdr1* gene, I have provided a quick, basic review below:

The MDR1 gene – A quick review **Sharon Vanderlip, D.V.M.**

mdr stands for Multiple Drug Resistance. The *mdr1* gene is responsible for encoding a large transmembrane protein called P-glycoprotein. P-glycoprotein plays an important role in transporting certain drugs through the protective blood brain barrier and back out of the brain, and into the capillaries. Some, *not all*, drugs are substrates for P-glycoprotein.

In 2003, Dr. Katrina Mealy of Washington State University published a paper explaining how a deletion mutation in the *mdr1* gene in some Collies prematurely terminated P-glycoprotein synthesis. Because it is a “deletion mutation”, some people use the term “mutant” (from the word “mutation”) and assign the allele lacking the ability to produce P-glycoprotein a minus sign (-). The term “normal” is commonly used for the allele (gene) capable of producing P-glycoprotein and assigned a plus sign (+).

Each animal receives one allele (gene) from each of its parents, so a Collie would have two alleles for the *mdr1* gene. Dogs that receive a “normal” *mdr1* gene from each parent are +/+ (homozygous normal). Dogs that receive a “normal” gene from one parent and a “mutant” gene

from the other parent are +/- (heterozygous). Dogs that receive a "mutant" gene from each parent are -/- (homozygous mutant).

Dr. Mealy reported that Collies that are homozygous for the deletion mutation (-/-) were *sensitive to certain P-glycoprotein substrate drugs*, such as ivermectin. When Collies that are homozygous for the *mdr1* gene deletion are given certain P-glycoprotein substrate drugs, they can develop prolonged nervous system problems and die.

Dr. Mealy reported that dogs that were homozygous normal (+/+), or heterozygous for the normal *mdr1* gene (+/-) did not display increased sensitivity.

A DNA test is available for you to test your Collie for the *mdr1* gene deletion:

http://www.vetmed.wsu.edu/depts-vcpl/

A list of drugs to avoid and more information may be found on Dr. Mealey's website:

http://www.vetmed.wsu.edu/depts-vcpl/

http://www.healthgene.com/canine/tests.asp?testcode=C142

Here are some helpful websites for additional information:

http://www.awca.net/drug.htm

Ihttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1636591

Here are some **Selected Publications** to help you learn more. From these you can obtain additional references leading to more scientific articles and formation:

Mealey KL, Bentjen SA, Gay JM, Cantor GH. Ivermectin sensitivity in collies is associated with a deletion mutation of the mdr1 gene. Pharmacogenetics. 2001 Nov;11(8):727-33.

Mealey KL, Northrup NC, Bentjen SA. Increased toxicity of P-glycoprotein-substrate chemotherapeutic agents in a dog with the MDR1 deletion mutation associated with ivermectin sensitivity. J Am Vet Med Assoc. 2003 Nov 15;223(10):1453-5, 1434.