Multi-Drug Resistance Gene in Herding Breeds

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Abstract

Multidrug Sensitivity in Dogs is a gene mutation where the MDR1 gene encodes P-glycoprotein. P-glycoprotein is a drug transport pump that is important in limiting the amount of drug that is absorbed and distributed into the brain. P-glycoprotein also aids in the excretion of drugs used in dogs. The affected dogs are not able to filter the drugs out of the brain as efficiently and can become toxic. Some of these problem drugs include ivermectin, butorphanol, loperamide, selamectin, milbemycin, buprenorphine, and doxycycline. This gene mutation is more common in herding breeds such as the Australian Shepherds, Miniature American Shepherds, Collies, Border Collies, German Shepherds, Whippets, and other Sheepdogs. To test for this gene mutation, a cheek swab or blood sample must be submitted to one of the many companies that test for it through DNA samples. Washington State University offers a patent protected diagnostic test and is a reliable source since they first discovered the mutation and established the testing. However, Paw Print Genetics is also a very reliable and trusted lab to test through. Other sources of testing include Gensol and VetGen.

INTRODUCTION

There are many dogs used to herd livestock and/or bred for the specific capability of herding. The herding group appointed by American Kennel Club is rather large and diverse with many breeds which are loved by owners across the world. Unfortunately, somewhere back in time, there was a mutation in a gene that effected many breeds from that point on and not only in herding breeds. This multi-drug resistance gene can be problematic for any dog owner who expects a veterinarian to take care of their dog or a dog owner who administers medication to their livestock. Livestock dewormers can cause a severe problem if dogs spend time around the pens or rangeland and ingest livestock feces.

It is important to know whether or not a herding or mixed breed dog is affected by this inconvenient and life-threatening mutation. If a dog has not been tested and is clearly a herding breed or herding mix, problem medications should be reduced in amount or avoided all together. Genetic testing is then recommended if the owner would prefer to know for a surety if their dog should avoid these medications, use them with caution, or use the medications without any unusual concerns.

Review of Literature

The Multi-Drug Resistance Gene encodes for a protein called the p-glycoprotein. When there is no mutation found in this gene, this protein is able to perform the tasks it is meant to. The tasks performed by this protein include limiting the absorption and the distribution of certain medications, particularly in the brain. Another task performed by this protein includes enhancing the excretion of medications. When we have a mutation in this gene, the dog becomes "affected" and can have issues limiting absorption, limiting distribution, and helping excrete many common medications used in companion animals and livestock. This mutation can cause dogs to become severely toxic if too much medication is given or ingested. **Figure 1** Depicts a simplified explanation from Wisdom Panel of what can happen in a mutated dog compared to a normal dog. Symptoms of neurological toxicity vary depending upon the drug that is given but can include seizures and in severe cases, coma and death.

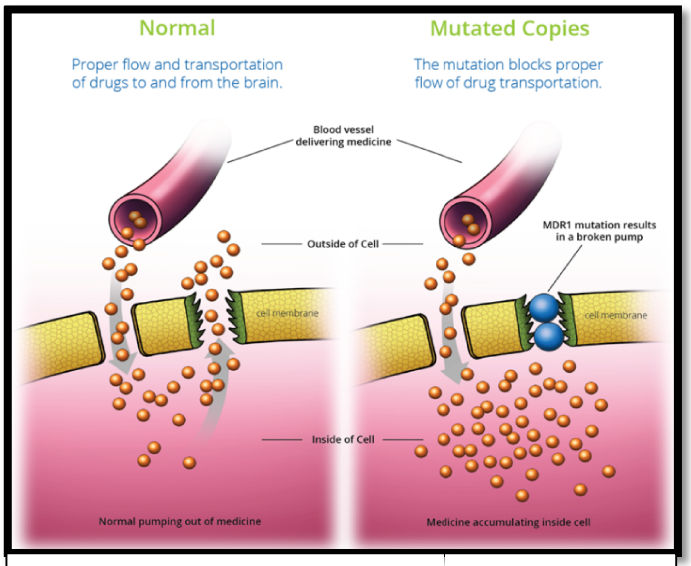

Figure 1 *- Comparison of Normal Vs Mutated Pumps*

(Source: Wisdom Panel)

The discovery of this gene involved an experiment with mice. The MRD1 gene is a common and important gene among mammals, including humans. A laboratory in the

Netherlands genetically engineered mice to remove the MRD1 gene in order to see the effects. After quite some time, the researchers did not see a difference between the control mice and experimental mice. The experimental mice were just as happy and reproduced as successfully as the control mice. However, eventually there was an infestation of mites among the mice colony. The laboratory technicians, as per protocol, sprayed the infestation with an ivermectin spray. The next day nearly all of the experimental mice were dead. Thus the sensitivity became evident and testing persisted. The Veterinary Clinical Pharmacology Lab (VCPL) at Washington State University was the first to discover this genetic mutation in dogs.

The MDR1 gene in dogs is inherited from the parents and is classified as autosomal (meaning that it resides on a chromosome that is not a sex chromosome such as 'X' and 'Y') and incompletely dominant (meaning there is not an allele that is dominant over another). This gene can be expressed by three different genotypes. The genotype N/N or Normal/Normal indicates that the tested dog does not have any copies for the mutation. Their drug transport pump is not affected and should work normally.

The next genotype possible includes results such as N/M or Normal/Mutant. This genotype indicates that the tested dog is a carrier of the mutation and has inherited a single copy of the mutation gene. Unlike many diseases, a carrier of the genetic defect results in an affected dog. This is due to the fact that it is incompletely dominant as discussed earlier. A dog with one allele can still react negatively to the medications that the p-glycoprotein pump is responsible for. The level at which carrier dogs are affected varies on an individual basis. There is not a set boundary at which they can no longer tolerate a certain medication (Miller).

The final genotype possible is M/M or Mutant/Mutant. This genotype is the most problematic and the most affected in terms of reactivity to medication. Toxicity will generally be more severe in a fully mutated dog than a carrier dog. Again, there is a lot of individual variation that takes place as to when a dog can no longer tolerate an amount of a medication. It is recommended not to breed a Mutant/Mutant dog with another dog who carries either one or two copies of the mutation. Therefore, no M/M dogs will be produced.

In regard to breeds that are at risk for this genetic mutation, it is easy to lump them together as "herding breeds" but that is not completely true. The majority are categorized as herding dogs but there are a few outside of this group. **Table 2** depicts breeds and the frequency of which they are recorded to be "affected" by VCPL.

Table 1 *- Breeds Affected and the Frequency (%)*

Breed	Freq.	Breed	Freq.
Collie	70%	Shetland Sheepdog	15%
Long-haired Whippet	65%	English Shepherd	15%
Australian Shepherd	50%	German Shepherd	10%
Mini Aussie/ Mini American Shep.	50%	Herding Breed Cross	10%
McNab	30%	Border Collie	5%
Silken Windhound	30%	Mixed Breed	5%

Data from VCPL, Washington State University

Following breeds affected by the mutation, our focus will turn toward medications that are considered a problem and are known to be affected by the p-glycoprotein drug pump. The list is quite extensive and can vary based on sources available. The VCPL at Washington State holds a lot of respect from dog owners and veterinary practitioners because of their discovery. As a result, most information will come directly from their research.

The first - and possibly most referenced problem medication - is ivermectin. Ivermectin is commonly used as an antiparasitic medication. It is found in Heartgard, Iverhart, Tri-heart Plus, and Ivomec. VCPL deems ivermectin to be safe if given the recommended dose unless treating for mange. The recommended dose for mange will cause nuerological toxicity in M/M dogs and can cause toxicity in N/M dogs. Ivomec is a medication containing ivermectin that is often given to livestock as a dewormer. If an affected dog ingests feces of a recently dewormed livestock animal, this can result in severe toxicity. If educated, many pet owners of breeds prone to the mutation will avoid this medication altogether including heartworm prevention.

Similarly, milbemycin, selamectin, and moxidectin are other antiparasitics. VCPL has also deemed all three medications to be safe in recommended doses. Toxicity has been recorded in doses 10-20 times the correct amount. For heartworm preventatives, milbemycin products are recommended over heartworm preventatives containing ivermectin.

Acepromazine, also referred to as acetylpromazine or Ace, is a commonly used medication. It is often given as a tranquilizer for stressful situations such as fireworks, lightening, long car rides, and grooming appointments. Acepromazine can also be used as a pre-anesthetic drug to be given prior to undergoing anesthesia. Acepromazine also can act as an anti-nausea. VCPL has determined that a drug reduction is indeed necessary in affected dogs. There is no information regarding as to how much it should be reduced.

Butorphanol, commonly known as Torbugesic, Torbutrol, or Dolorex, is a medication commonly given as pre-anesthetic medication and as an analgesic. It can be used to alleviate

coughing and pain (DiamondBack Drugs). VCPL recommends reducing the dose of butorphanol in affected dogs. No amount has been given to determine a safe dose.

Buprenorphine, also known as Cizdol, Buprenex, and Temgesic, is given to manage moderate pain. Morphine is also classified very similarly. These drugs are known to be filtered by the p-glycoprotein pump in humans but appear to be safe in dogs since no cases of toxicity have been reported by collaborative research.

Loperamide, also referred to as Immodium, is occasionally given to dogs to treat diarrhea. At the dose recommended for this treatment, it will cause neurological toxicity in affected dogs. VCPL recommends that this drug should be avoided in all dogs with any form of the mutation. Untested dogs should avoid loperamide.

Vinblastine, Vincristine, Doxorubicin, and Paclitaxel are all chemotherapy agents that VCPL has determined to require dose reductions. If a dose isn't reduced, a dog may become severely toxic. Again, there is not a recommended amount by which to reduce the dose.

Cyclosporin (immunosuppressive agent), Digoxin (cardiac drug), and Doxycycline (antibacterial drug) are all reported by VCPL to be pumped out of the brain by the MDR1 gene but have not appeared to cause an increase in sensitivity compared to unaffected dogs. VCPL does not recommend reducing the correct dose but suggests to monitor use. Other medications VCPL encourages to be cautious while administering include the following: domperidone, etoposide, mitoxantrone, ondansetron, and rifampicin.

There are several ways to test canines for this genetic mutation in order to make safe and comfortable decisions when administering medication. The easiest way to test includes ordering a cheek swab packet from a laboratory of your choice. Once the packet is received, directions are followed with the provided equipment in order to obtain cheek cells from the canine being tested. The packet is sent back, usually by mail, and processed at the lab for the next couple weeks before results are reported to the owner. Another method by which to test includes obtaining a blood sample. This is usually a less preferred method as a veterinarian should collect the sample.

VCPL at Washington State University provides a patent-protected test for this genetic mutation. PawPrint Genetics is another well-known and respected laboratory which offers hundreds of genetic disease and trait tests. PawPrint genetics tests their samples using two methods to ensure accuracy (Shaffer). There are other labs which offer this service; some of which include Wisdom Panel, Gensol, VetGen and Animal Genetics. Prices vary but are usually within the $50 to $80 range.

SUMMARY

In conclusion, if a dog is labeled as a breed or mixed breed prone to a mutation in the MDR1 gene, it is highly recommended to test the dog to determine the genotype. After receiving results, the owner can better understand the degree to which he or she should be cautious when administering certain medications known to be filtered by the associated protein. Results involving one or two mutations are therefore affected and should be treated very carefully. Not all veterinarians are aware of the mutation and which medications are to be avoided or reduced. For clients at a veterinary hospital, it is a great idea to print a list of problematic medications as well as the dog's genotype and give it to a veterinarian to keep in the patient's file. This is a helpful way to educate practitioners and technicians who are less aware of the mutation.

Along with education, responsible breeders of any of the affected breeds should genetically test breeding stock to avoid producing a plethora of dogs with the mutation. In some breeds where the mutation frequency is higher, it is discouraged to remove all affected dogs from breeding as this would decrease the genetic pool significantly. However, eventually breeding this genetic mutation out of a breeding stock while keeping other desired traits helps many dogs and their loving owners for the future.

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APPENDIX

Title Page: Illustration.

This illustration depicts an Australian Shepherd which is a breed with a high frequency of inheriting the MDR1 mutation.

Source: http://www.akc.org/dog-breeds/australian-shepherd/

Figure 1: Comparison of Normal Vs Mutated Copies

This diagram is a simplified comparison between p-glycoprotein pumps inherited normally versus pumps inherited with a mutation. Unlike a normal gene, the mutation copy blocks proper distribution of medications. The medication then accumulates inside cells and causes toxicity.

Source: http://www.wisdompanel.com/mdr1_disease_screening/

Table 2: Data from VCPL, Washington State.

This table demonstrates which breeds are commonly seen with this genetic mutation and the frequency (in percent) they are seen. The animals included in the data are "affected", meaning they could carry either one or two copies of the mutation. As noticeable from the chart, not all breeds are categorized as herding dogs.

Source: http://vcpl.vetmed.wsu.edu/affected-breeds