Canine Genetic Mutations to the Multi Drug Resistance Gene (MDR1)

Background
More than 100 years ago, research showed that certain chemical dyes injected into the peripheral circulation infiltrated most organs, with one exception – the brain. This led to the well-known concept of a blood-brain barrier. Research in the early 1960s showed that the basis of the blood-brain barrier is the specialised endothelial cells of brain capillaries. A number of active transport systems exist that selectively regulate both influx and efflux of compounds across brain capillary endothelial cells. The most important drug-efflux system of the blood-brain barrier identified to date is P-glycoprotein, P-gp.

The product of the mdr1 (multidrug resistance) gene is P-glycoprotein, a cell-surface protein that functions as a drug-efflux pump. P-glycoprotein was first identified over 20 years ago in chemotherapeutic drug-resistant tumour cells, and is now known to be a major cause of multidrug resistance in human and veterinary cancer patients, including dogs. In tumour cells, P-glycoprotein functions as an ATP-dependent efflux pump, resulting in decreased intracellular drug accumulation and reduced cytotoxicity.

In certain canine breeds, particularly herding breeds, a mutation occurs in the MDR1 gene which reduces the function of the gene, causing sensitivity to a number of commonly prescribed drugs such as ivermectin and loperamide. Dogs with this mutation have a defect in the P-glycoprotein that is normally responsible for transporting certain drugs out of the brain. The defective protein inhibits the dog's ability to remove these drugs from the brain, leading to a buildup of these toxins. As a result of the accumulation of toxins, the dog can show neurological symptoms, including seizures, blindness, ataxia, coma or even death.

In 2001, a research team at Washington State University, led by Dr Katrina Mealey and Steven Bentjen, uncovered a four base pair deletion in the MDR1 gene. This deletion results in the production of truncated and non-functional P-gp and thereby causes sensitivity to ivermectin and other drugs that serve as P-gp substrates.

Drugs that May Cause Toxicity in Affected Dogs
Dogs with this genetic mutation can be much more sensitive to certain drugs. A dose that is not normally harmful can be toxic or deadly to an affected dog. The list of potentially problematic drugs includes a wide range of medications including anti-parasites, cancer drugs, sedatives, anti-diarrhea, pain medications and heart drugs. Some of the drugs that should be avoided by affected dogs include: ivermectin (found in heartworm and anti-parasite medications), milbemycin, moxidectin and selamectin (anti-parasite), loperamide (Imodium over-the-counter antidiarrheal agent) doxorubicin, vincristine, vinblastine (anticancer agents) acepromazine (tranquiliser) butorphanol (pain control), erythromycin (antibiotics), and emodepside (dewormer).

There are additional drugs that may also cause problems including morphine, cyclosporin, digoxin, rifampin, ondansetron, domperidone, paclitaxel, mitoxantrone, etoposide, rifampicin and quinidine.

Many of the problematic drugs are very commonly prescribed. For example, ivermectin is found in canine heartworm prevention, worming and anti-mange medications. Additionally, the drug is used to prevent parasites in horses and livestock. While the amount of ivermectin found in a normal dose of heartworm prevention medication should not be a concern, larger doses of ivermectin, such as the amount used to control mange or for worming, can have serious effects. Dogs with the MDR1 mutation will need to be kept away from horses or livestock that have been given ivermectin because the drug will remain in their faeces. If the dog ingests the faeces, it can become ill.

Symptoms of MDR1 Gene Mutation
The specific symptoms of MDR1 toxicity depend on the specific drug and the amount of the drug that has been ingested, but can include problems with balance and coordination, drooling, stupor, blindness, behavioural changes, tremors, vomiting, coma and even death in some cases.

Canine Breeds that Are Most Likely to Carry the Mutation
Breeds that are more likely to have a MDR1 mutation are Australian Shepherd, Border Collie, Collie, English Shepherd, McNab Shepherd (McNab Border Collie), Old English Sheepdog, Shetland Sheepdog (Sheltie), Silken Windhound, Rough Collie, Smooth Collie, German Shepherd, Bobtail, American White Shepherd and Longhaired Whippet. It appears that Australian Shepherds, Collies and Longhaired Whippets have the highest probability of carrying the mutation. Collies in particular are likely to carry the mutation – estimates are as high as 70% of the Collie population. Longhaired Whippets are also likely to be affected – estimates are about 65% of the population. The likelihood of an Australian Shepherd carrying the mutation is also high – approximately half of Australian Shepherds will have the mutation.

Mixed breeds with herding dog ancestry can also be at risk of carrying the mutation. Since it is not always obvious what the parentage is for mixed breed dogs, testing is advisable before giving high doses of the potentially problematic drugs.

Test Before Administering Drugs

Testing a dog for the MDR1 genetic mutation will let the owner know if their dog should avoid certain drugs or should have lower doses of the problematic drugs. If a dog tests positive for the mutation, alternative drugs can be used or lower doses can be prescribed. Tests are conducted using samples of DNA collected from the cheeks, blood or dewclaws. You do not have to visit a veterinarian to collect samples or process the tests. You simply need to collect the DNA and mail in your sample to be tested. If a dog does test positive for the MDR1 mutation, you will need to inform your veterinarian. Medical alert tags for MDR1 mutation are also available.

Breeding Considerations

A dog may have zero, one or two copies of the genetic mutation. A dog with either one or two copies of the mutation is considered to be "affected." If a dog has two copies of the mutation, it will have sensitivity to the drugs and will pass a copy of the mutation to any offspring. Dogs that have one copy of the mutation may still be sensitive to the problem drugs in high doses and will have a 50 % chance of passing on the mutation to offspring.

The ideal situation would be to breed dogs that have zero copies of the mutation, but this is not practical for breeds with a high likelihood of carrying the defect, such as Collies. In this situation, testing can help breeders identify affected dogs and breed accordingly. Since the condition is not an issue if problem drugs are avoided, it is not necessary to remove affected dogs from the breeding pool. But being aware of the genetic profile of a particular dog can help to gradually reduce the number of affected dogs in the breed.

Breeding Chart

	Normal/Normal Male	Normal/Mutated Male	Mutated/Mutated Male
Normal/Normal Female	100% Normal/Normal puppies	50% Normal/Normal 50% Normal/Mutant puppies	100% Normal/Mutant puppies
Normal/Mutated Female	50% Normal/Mutant 50% Normal/Normal puppies	50% Normal/Normal 25% Normal/Mutant 25% Mutant/Mutant puppies	50% Normal/Mutant 50% Mutant/Mutant puppies
Mutated/Mutated Female	100% Normal/Mutant puppies	50% Normal/Mutant 50% Mutant/Mutant puppies	100% Mutant/Mutant puppies

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