



Sibling Survivors. Cheeto and Frito, both with *MDR1* mutant/mutant genotypes, survived adverse reactions to an eprinomectin-containing product.

Topic Overview

This article describes how the multidrug-resistance 1 (*MDR1*) gene mutation in cats affects P-glycoprotein, the effects of P-glycoprotein substrate drugs on cats with the mutation, and the value of testing cats for the *MDR1* mutation.

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INTERNAL MEDICINE

Multidrug-Resistance 1 (*MDR1*) Mutation in Cats

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A multidrug-resistance 1 (*MDR1*) gene, also known as adenosine triphosphate-binding cassette transporter subfamily B member 1 (*ABCB1*), was discovered in dogs in 2001¹ and in cats in 2015.² Although the *MDR1* mutation itself differs between dogs and cats, the clinical implications are the same. Less information, however, is available regarding the mutation in cats.

Originally called ivermectin sensitivity in collies, the predisposition of collies to experience adverse reactions to ivermectin led to the discovery of the gene mutation.¹ In dogs, the *MDR1* mutation can be traced back to herding breed ancestry.³ Today, the mutation is still most prevalent in herding breeds, such as collies and Australian shepherds. Other breeds affected include German shepherds, Shetland sheepdogs, and border collies.⁴

After neurologic toxicity in cats that had received ivermectin was reported, researchers examined the *MDR1* gene and identified a mutation that differed in genetic makeup from that in dogs. For cats, however, the history of the mutation is unknown.

In 2022, according to the AVMA, approximately 7% of cat owners purchased their cat from a breeder,⁵ which means that 93% of owners adopted their cats from shelters or friends or found them as strays. Thus, because most pet cats in the United States are adopted, it is not possible to trace their genetics. Additionally, millions of cats without owners live and breed on their own, making it impossible to control which cats reproduce and which genes they pass on. Despite this uncertainty, it is known that incidence of the *MDR1* mutation is higher among Maine Coon cats than among

Learning Objectives

- There are no physical indicators of which cats could have the multidrug-resistance 1 (*MDR1*) genetic mutation.
- The *MDR1* mutation is associated with P-glycoprotein dysfunction, which can lead to toxic accumulation of certain drugs and neurologic signs in cats.
- Animals with the *MDR1* mutation are generally healthy unless or until they receive a P-glycoprotein substrate drug.
- P-glycoprotein substrate drugs known at this time include, but are not limited to, macrocyclic lactones, some chemotherapy drugs, and some sedatives.
- Testing cats for the *MDR1* mutation should become a routine part of new-patient screening and should be performed before P-glycoprotein substrate drugs are administered.
- Cats that experience an adverse reaction need correct treatment that avoids making symptoms worse.



other purebred cats and that mixed-breed cats (i.e., domestic short-, medium-, and long-haired cats) are affected.⁶ Among domestic cats overall, the *MDR1* mutation is found in 1% to 4%,² which means that 738 000 of the 73.8 million cats in the United States could have the *MDR1* mutation.⁷ On a smaller scale, this prevalence rate means that if a veterinary clinic sees 100 cats per week, 1 or more of those cats is likely to have the *MDR1* mutation (**FIGURE 1**).

THE *MDR1* GENE MUTATION AND DRUG SAFETY

The *MDR1* genetic mutation disrupts the function of P-glycoprotein, a protein that acts as an efflux pump to remove foreign substances (e.g., drugs) from cells, particularly endothelial cells of blood vessels and cells of the brain and liver.⁸ The absence of P-glycoproteins makes animals susceptible to adverse reactions from drugs that are not transported out of essential organs.

Drugs that are removed by P-glycoprotein are called P-glycoprotein substrates. P-glycoprotein substrate drugs used in cats include macrocyclic lactones, chemotherapeutic agents, and sedatives. Because the *MDR1* mutation severely blunts P-glycoprotein's ability to transport drugs from essential organs, P-glycoprotein substrates can accumulate with dangerous and possibly deadly consequences. If P-glycoprotein cannot remove the substrates from the brain (through the blood-brain barrier and into the bloodstream), their accumulation in the brain can lead to neurologic signs. For patients with the *MDR1* mutation, P-glycoprotein substrate medications should be avoided or dosages should be modified.⁹ Dosing modifications depend on multiple factors, including the patient's health status, concurrent medications, and the specific *MDR1* genotype (*MDR1* mutant/mutant, mutant/normal, normal/normal; see ***MDR1* TERMINOLOGY**).

For patients with the *MDR1* mutation, P-glycoprotein substrate medications should be avoided or dosages should be modified.⁹



CONSEQUENCES OF ADMINISTERING A P-GLYCOPROTEIN SUBSTRATE TO CATS WITH THE *MDR1* MUTATION

Some of the most common P-glycoprotein substrates used in veterinary medicine are macrocyclic lactones.¹⁰ Examples of those used as parasiticides for cats are ivermectin, eprinomectin, selamectin, milbemycin oxime, and moxidectin. Reports of eprinomectin toxicosis in *MDR1* mutant/mutant cats describe ataxia, tremors, lateral recumbency, mydriasis, and tongue protrusion.¹¹ Affected cats cannot eat or drink normally. If these signs are noted after macrocyclic lactone administration, care should be taken to not make the situation worse. Additional P-glycoprotein substrates can have a cumulative effect on the central nervous system and lead to a worsening of clinical signs, coma, and possibly death. Supportive therapy is essential, and the recovery period can be lengthy and expensive, making treatment cost prohibitive.¹⁰ Testing for the *MDR1* gene mutation before administering macrocyclic lactone products circumvents the risk for adverse effects and saves money in the long run.

Other P-glycoprotein substrates include some chemotherapeutic agents,¹² which can lead to neutropenia, thrombocytopenia, vomiting, and diarrhea in animals with the *MDR1* gene mutation, delaying much-needed therapy when time is crucial. It is better to test a cat before treatment and modify the dosages than to risk potentially life-threatening adverse effects in an already compromised patient.

Much of what is currently recommended for drug safety with respect to P-glycoprotein comes from research in dogs with the *MDR1* mutation, but it is reasonable to apply this knowledge to cats. For example, some commonly used sedatives in dogs are P-glycoprotein substrates, such as butorphanol and acepromazine.⁹ Another P-glycoprotein substrate used in dogs is maropitant, which is widely used for prophylactic treatment of nausea and vomiting.¹³ Although these medications have not been tested in cats with the *MDR1* gene mutation, it is reasonable to use caution when administering them to cats, especially if the drugs are used in conjunction with other P-glycoprotein substrates. Some P-glycoprotein substrates are not as strong as others, so the effects might not be as obvious, but when a P-glycoprotein substrate is combined with another, the results can be more profound. Anecdotally, some owners have reported that their pet was lethargic or seemed "off" or

“not themselves” while receiving maropitant (a weaker P-glycoprotein substrate) but returned to normal as soon as maropitant was discontinued.

DETECTING PATIENTS WITH THE *MDR1* MUTATION

Unlike dogs, for which more than 50% of some breeds are affected,⁴ there are no strong breed predilections for cats or ways to predict which cats might have the *MDR1* mutation. The only way to know if a cat has the *MDR1* mutation is testing (genotyping), which should be offered as part of every cat’s health screening, especially those that will receive parasiticides. An easy, widely available, and affordable (\$70) test is available through the Washington State University College of Veterinary Medicine Program in Individualized Medicine (PrIME; go.navc.com/4INbYdF) and can be performed by clients at home (cheek swab sample) or in the clinic (blood or DNA collection brush sample)

before any potentially toxic medication is given to a healthy cat.

The lack of physical characteristics associated with the *MDR1* mutation in cats and the lack of information on drug labels regarding their P-glycoprotein substrate status increases the risk for serious adverse drug reactions. Some P-glycoprotein substrate drugs in one species might be applicable to another species but also may differ among species. It is conceivable that P-glycoprotein substrates for dogs or humans could be P-glycoprotein substrates for cats.⁹

Among new drugs continually being developed and marketed for dogs and cats, most are not assessed for P-glycoprotein substrate status. Thus, prescribing medication for cats with an unknown *MDR1* genotype can be risky. In 2023, a new parasiticide containing eprinomectin was introduced to the market, after which increased adverse reactions were noticed in



FIGURE 1. Locations of cats tested at the Washington State University Veterinary Clinical Pharmacology Laboratory and determined to have the multidrug-resistance 1 mutation, showing widespread distribution.

An animal with only 1 copy of the genetic mutation will not be affected as severely as an animal with 2 copies but still can experience adverse effects if drug doses are not reduced.



MDR1 mutant/mutant cats. Many young, healthy cats experienced neurologic effects for weeks and subsequently died. Thus, the key to preventing P-glycoprotein-mediated adverse drug reactions is determining the genotype of feline patients before administering potentially harmful medications.

One source for problem medications for cats with the *MDR1* mutation can be found at go.navc.com/4IRHpDD. This list is not exhaustive as new drugs are being tested on an ongoing basis. A few examples of drugs currently being tested are cisapride, cyclosporine A, and methylprednisolone. The FDA recommends determining the P-glycoprotein substrate status of drugs before the drug is marketed for use in humans, but the same requirement does not exist for drugs for animals.¹⁴ Veterinary pharmaceutical companies do not perform this testing; however, testing is being performed at the Washington State University Veterinary Clinical Pharmacology Laboratory and is funded by the EveryCat Health Foundation

(everycat.org). Organizations must rely on private donors or grants to support the testing of possible P-glycoprotein substrates for cats. After results from testing are peer-reviewed and published, P-glycoprotein substrates are added to the problem medications list on the Washington State University website listed previously. It is hoped that in the future drug companies will begin to test medications for P-glycoprotein status before they are released for use in veterinary medicine. Such a preventive measure could supply veterinary professionals with valuable information and avoid many adverse reactions in patients with the *MDR1* mutation.

MDR1 TERMINOLOGY

An animal inherits 2 copies of the *MDR1* gene, 1 from each parent, which is relevant as many clients report that their dog or cat is “positive for *MDR1*,” which is incorrect because the *MDR1* gene exists in every cat and dog (**FIGURE 2**). It is the *MDR1* gene mutation that causes problems.

- For animals with 2 copies of the *MDR1* gene mutation, the preferred terminology is “*MDR1* mutant/mutant.”
- For animals with only 1 copy of the *MDR1* gene mutation, the preferred terminology is “*MDR1* mutant/normal.”
- For animals with no *MDR1* gene mutation, the preferred terminology is “*MDR1* normal/normal.”

The *MDR1* gene mutation is considered a dominant mutation, meaning that an animal with only 1 copy of the genetic mutation experiences susceptibility to adverse effects from P-glycoprotein substrates. The

<i>MDR1</i> Genotype Combinations	Mutant/Mutant	Mutant/Normal	Normal/Normal
Mutant/Mutant	Mutant/Mutant	Mutant/Mutant	Mutant/Normal
		Mutant/Normal	
Mutant/Normal	Mutant/Normal	Normal/Normal	Normal/Normal
	Mutant/Mutant	Mutant/Normal	Mutant/Normal
Normal/Normal	Mutant/Normal	Normal/Normal	Normal/Normal
		Mutant/Normal	

FIGURE 2. Punnett square showing genotype combinations of the multidrug-resistance 1 (*MDR1*) genotypes.



FIGURE 3. Cat with the multidrug-resistance 1 mutation as identified at Washington State University's Veterinary Clinical Pharmacology Laboratory.

term “carrier” is also incorrect in that it implies that the animal is not affected and is only able to pass the gene to offspring. An animal with only 1 copy of the genetic mutation will not be affected as severely as an animal with 2 copies but can still experience adverse effects if drug doses are not reduced.

HYPOTHETICAL CASE SCENARIO

One morning, a 9-month-old intact male domestic shorthair kitten is taken to an emergency veterinary hospital due to neck ventroflexion and lateral recumbency. Examination further determines that he also has mydriasis with no palpebral reflex and tongue protrusion. The client states that the kitten started to “walk funny” last night and that they found him in this condition in the morning. Coincidentally, he had been seen at his local veterinary clinic the day before for a kitten wellness examination. He was a perfectly healthy, playful kitten. He received his last set of vaccinations and an application of parasiticide at the office visit. The kitten was fine when he left the hospital the day before. His full sibling in the same household received the same treatments. The cats were kept separate after the application of the parasiticide to prevent unintentional oral ingestion of the topical parasiticide by grooming. The sibling did not exhibit any clinical signs.

This scenario is a classic presentation of a cat that is homozygous for the *MDR1* genetic mutation and is experiencing an adverse reaction to an eprinomectin-containing parasiticide. Time and supportive therapy, specifically hydration and nutritional support, are needed to help cats clear the eprinomectin from the

brain, but equally valuable is avoiding drug treatments that exacerbate the neurologic toxicosis.

COMMUNICATING WITH CLIENTS

Explaining the *MDR1* genetic mutation and its consequences to clients during their cat's yearly examination might encourage them to test their cats for the *MDR1* genetic mutation. Owners should be informed that the genetic mutation makes cats more susceptible to adverse reactions to certain medications, including some parasiticides, anesthetics, anti-nausea drugs, and chemotherapeutic agents. Clients should also be informed that there are no physical predictors, such as breed or coat color, for the mutation (**FIGURE 3**) and that testing is the only way to determine a cat's *MDR1* genotype.

SUMMARY

Knowing a patient's *MDR1* genotype could be lifesaving for both preventing and treating adverse reactions to P-glycoprotein substrates. Unfortunately, the *MDR1* mutation is often diagnosed after a cat experiences an adverse drug reaction rather than during genotyping performed before drug administration. The author is aware of many situations in which the mutation was discovered too late and the cat died or was euthanized due to the severity of the adverse drug reaction. Cats can, and have, fully recovered from the insult if given time and appropriate supportive medical management. Testing for the *MDR1* gene mutation should be added to the tests offered to clients to ensure that patients are not inadvertently harmed by measures designed to protect them. **TVN**

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Jennifer graduated from Bel-Rea Institute of Animal Technology in 1994 and began working at Washington State University in 1995. While taking time off to raise children, she finished a bachelor's degree in social science from Washington State University. Jennifer resumed her career as a veterinary technician at Washington State University in 2013 and worked in various departments in the Veterinary Teaching Hospital. Jennifer recently moved to the veterinary clinical sciences department and works in the Veterinary Clinical Pharmacology Laboratory as a clinical studies coordinator. Jennifer's recent work with cats with the multidrug-resistance 1 (MDR1) gene mutation experiencing adverse reactions, along with her communication with their veterinarians and clients, has made her dedicated to increasing awareness about cats with the *MDR1* genetic mutation.



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1. **P-glycoprotein transports drugs into the brain through the blood-brain barrier.**
 - a. True
 - b. False
2. **Why is it important to recognize the clinical signs of a cat with the *MDR1* gene mutation that could be experiencing an adverse reaction?**
 - a. The *MDR1* gene mutation makes the cat resistant to certain treatments.
 - b. You could make the cat worse by giving drugs that could cause a cumulative effect.
 - c. You need to know which diagnostic tests to perform.
 - d. The cat is highly contagious.
3. **Testing for the *MDR1* gene mutation in cats is not often done because:**
 - a. It is expensive.
 - b. It is hard to acquire.
 - c. There is a lack of awareness.
 - d. There is no reason to test cats.
4. **P-glycoprotein substrates include:**
 - a. Macrocyclic lactones
 - b. Some sedatives
 - c. Some chemotherapeutic drugs
 - d. Some antinausea medications
 - e. All the above
5. **The most common clinical signs exhibited by a cat homozygous for the *MDR1* gene mutation (mutant/mutant) that is experiencing an adverse reaction to eprinomectin include:**
 - a. Vomiting/diarrhea
 - b. Incontinence
 - c. Seizures
 - d. Ataxia, mydriasis, tremors, and tongue protrusion