**Understanding the Frequency of the MDR1 Mutation Among Purebred Canines**

**Outline**

***Background*** A mutation occurring in what is known as the canine multidrug resistance gene results in a receptor causing what is known as ivermectin toxicity for canines given ivermectin1,2. Ivermectin acts as a parasiticide that kills roundworms and some species of arthropods that affect canines. However, when given the drug, the impact on the canine causes neurological symptoms and potentially fatal results1.

***Research*** Information was gathered from two research documents, the first being: *Genotypic and allelic frequencies of the MDR1 gene in dogs in Italy*, studying the direct number of individuals of the trait in Italy. The second is *Breed distribution and history of canine MDR1-1Δ. This pharmacogenetic mutation marks the emergence of breeds from the collie lineage*, studying both the history of the mutation and the overall individuals affected by it.

***Results*** The mutation appears to be more common in purebred canines deriving from collie ancestry but appearing in what is likely the common ancestor of the collie lineage and other related lineages1,2.

***Conclusion*** The mutation does not appear to be apparent in the more significant portion of purebred canine breeds; however, several canines concerning the collie lineage may be at risk of obtaining the mutation.

**Background**

Ivermectin toxicity occurs once ivermectin has been administered to the body. This is because the drug reacts with receptors of the mutated MDR1 gene leading to dysfunction of how well a drug interacts with the body. In time, this causes abnormal neurological symptoms in the body and potentially leads to comatose or fatality1. In a normal situation, the gene helps assist proteins in preventing drugs from reducing the effects of drugs on the central nervous system1. During previous investigations into the origin of the mutation, it had been suspected that primarily purebreds deriving from collie lineage were affected; however, further analysis suggests that breeds that do not appear to have collie ancestries, such as sighthounds, shepherds, and sheepdogs1,2.

The present paper is an investigation as to just how widespread among purebred breeds the mutation. While not every individual in a breed is affected by the mutation, a better understanding of how many canines are overall affected by the trait would allow for better medicinal consciousness when administering ivermectin. Two studies were selected for research on the assignment, which studied the genomic makeup of individuals participating in the studies and helped observe reasoning as to why the results occurred.

**Research**

According to two studies, one conducted in the United States and another conducted in Italy, DNA information was collected from different purebred canines. To accommodate variety, blood and salivary samples were taken from canines through volunteer efforts and amassed a large variety of purebreds from different groups and backgrounds1,2. Samples from both studies were sent to laboratories to conduct experiments on each sample dealing with primers. The primers experimented with were designed to help locate the mutation in MDR11,2. When completed, both tests recorded the information and compared it with other breeds sampled to help conclude an answer. The tests

**Results**

According to the Italian study, the highest mutation frequency occurred in those with collie lineage, with the highest percentage in the ascertained samples ranging from seventy-five to thirty-five percent of the total breed. These percentages included the Smooth Collie, the Rough Collie, and the Australian Shepherd, represented in descending order. The Shetland Sheepdog followed, representing six percent of the breed's samples affected by the mutation. Border Collies and Bearded Collies were shown to have no affected percentage. However, evidence suggests that the collected specimens were carriers for the mutation. These comprised the main breeds typically afflicted with the mutation1.

Two other breeds commonly have the affected mutation, known as the Old English Sheepdog and White Swiss Shepherd Dog representing eight and seven percent being affected, respectively. The Whippet, a sighthound, finished the primary findings with ten percent being affected with the MDR1 mutation1. Concluding the Italian study results, the twenty-two other breeds did not show any form of mutation in their genomic information1.

According to the American study, more than 4,000 samples were provided from purebred canines for the survey. The result was that nine breeds that participated had the MDR1 mutation present. The rest of the breeds present, those who primarily traced their origins to continental Europe, appeared to lack the mutation; however, the Longhaired Whippet and Silken Windhound were both shown to have the MDR1 attribute2.

The mutation frequency was measured for each affected breed population which rated differently2. Surprisingly, the results of this test proved to be similar to that of the Italian study. As expected, collies made the most considerable portion of those afflicted with the mutation, but breeds like sheepdogs and sighthounds also had a slight appearance of the mutation. According to the researchers, the study was biased to help identify the relatedness between various breeds to pin down the ‘commonness’ of the mutation2. Despite this, the results of this study coincide relatively equally with the study composed in Italy.

**Conclusion**

Based on the information found in the two studies, most other purebred canines do not carry the trait. Instead, this is a genomic mutation that occurs primarily in a lineage in correlation to collies1,2. The trouble remains as to how and why other breeds that are not collie descendants represent breeds that are known for having this mutation.

According to the researchers conducting the American study, most breeds that represent the MDR1 mutation trait appear to originate from Great Britain. Therefore, it is suspected that a shared ancestry between the collie lineage and those of other breeds, like sheepdogs and sighthounds, is to blame. However, there is also the possibility that original thoughts about the family correlation between the groups are more closely related than once thought. Based on a study of the chromosomes of the afflicted breeds, it would appear that sighthounds only gained the mutation recently. At the same time, collies and sheepdogs have had the mutation for many generations. This suggests that the sheepdog diverged from collies many generations ago while some of the affected sighthounds, being relatively newer, carry the traits from mixing multiple breeds with a variant of collie lineage. As this new lineage is young and continues to be in-bred, the present mutation only continues to be present2.

It is essential to understand that the further breeders go with creating new dog breeds and try to create a standard via in-breeding, there is an increased risk of mutations. Furthermore, more breeders use those that carry the MDR1 mutation to create their new breeds, and there is an increased risk of canines being affected by ivermectin toxicity. However, as research continues, more drugs negatively affect the MDR1 mutation present2.

It is essential to understand just how widespread the mutation is. With that knowledge, scientists and veterinarians should be able to narrow down a way to navigate or work with the new mutation. Veterinary medicine is limited in providing proven safe, and populous medications to help an ailing patient. Without the knowledge of how to work with the mutation, many patients affected by various illnesses may be at risk of suffering or preemptive humane euthanasia because of the inability to treat them. The more research being conducted and testing on those affected by the mutation that occurs, the closer there may be to answers as to how to work with this genomic anomaly.

**Acknowledgments**

1. Marelli, S. P. *et al.* Genotypic and allelic frequencies of MDR1 gene in dogs in Italy. *National Library of Medicine* (2020). <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7319724/>
2. Neff, M. W. *et al.* Breed distribution and history of canine *MDR1-1Δ*, a pharmacogenetic mutation that marks the emergence of breeds from the collie lineage. *Proceedings of the National Academy of Sciences* **101,** 11725–11730 (2004).