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Editorial

Genetic Carrier Screening in Domestic Dog Breeds

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EDITORIAL

The sequencing of the canine genome [1] and the development of advance molecular technologies has dramatically enabled the identification of disease-associated mutations that can be utilized in preconception screening in breeding programs and for making a definitive diagnosis in symptomatic dogs. Approximately 150 disease-associated mutations are known in the domestic dog [2]. Although some disease mutations occur in a single breed, many occur in several breeds either indicating a single ancestral founder with the mutation or crossbreeding between breeds with the mutation prior to the designation of the founder stock. Once a foundation stock has been designated, crossbreeding between breeds usually ceases in order to establish the desired physical and behavioral characteristics for that specific breed. The presence and frequencies of specific mutations and their association with disease varies among the different dog breeds depending on when the mutation occurred during breed development.

Artificial selection for desired traits within certain breeds has inadvertently also fixed deleterious disease-associated mutations in these populations. Depending on the breed and disease, frequencies of carriers range from common to exceedingly, but measurably, rare. For example, depending on the populations surveyed, centronuclear myopathy in Labrador retrievers has a carrier frequency of 13.9% [3], while ichthyosis carrier frequencies in golden retrievers is about 44% [4]. Many individual mutations would be considered too rare to screen for routinely. However, because many breeds have several common mutations, new high-throughput molecular technologies allow the breeder to easily interrogate all known mutations in their breeding stock.

Most breed clubs have established health-screening guidelines that include veterinary exams for hips, elbows and eyes, and for some, genetic screening for disease-associated DNA mutations that occur in their breed. Within a breed club, there may be debate as to which disease-associated mutations should be screened and recommendations may change over time as diseases become more prevalent, or conversely, eradicated through careful breeding programs. Rare breeds, with fewer available individuals for breeding, are at a greater risk of increasing the frequency of disease within their populations [5]. Given the accuracy to which mutations can be identified and the new molecular methodologies that can control costs for the breeder, breed clubs should be discouraged from "cherry-picking" among diseases and encouraged to screen for all known mutations to eliminate certain mutations from their populations while monitoring the frequency of rarer mutations to prevent unintentional rise over time while selectively breeding for other traits.

Dams and sires used in breeding programs should, at a minimum, be screened for all mutations known for that breed. This can be accomplished in a panel or multiplex approach that is cost effective for the breeder. Two individuals carrying the same recessive mutation should not be bred as to protect against disease occurring in the offspring. When a carrier is bred to a homozygous wild-type (or clear) mate, approximately half of the offspring are expected to be heterozygous carriers. These offspring should be screened for all of the mutations carried by the parents and any carriers should be bred only to clear individuals in the future. Such responsible breeding can retain the desired physical and behavioral characteristics while controlling for the occurrence and spread of inherited diseases within the breed.

Ideally, the breeder should perform carrier screening on the dam and sire prior to breeding. However, genetic testing may occur at any time and veterinarians and dog owners should consider screening if it was not done previously on the parents or the new dog. In theory, dogs that are "clear by parentage" should not need to be tested, but in our experience, miscommunications among breeder and buyer or lost laboratory documentation has occurred and "clear by parentage" dogs have been shown to be carriers of disease. Currently, the majority of screening happens at the breeder's home or veterinary office, where cheek swab or blood specimens are collected for testing. Veterinarians should play an important role as advocates for the dog, new owners and breeders by recommending testing if not performed prior. For purebred dogs, new puppy exams should include information about inherited diseases in their breed. For mixed-breed dogs, discussion about common mutations that occur in multiple breeds is important because some diseases, such as degenerative myelopathy, which occurs in at least 124 breeds [6], can therefore also be disease-causing in mix-breed dogs.

Resources are becoming more available to breeders, dog owners and veterinarians to help navigate the complexity of the information provided in genetic screening. Genetic counseling

can help individuals understand that some diseases may have mild phenotypes, variable expression, low penetrance and/or varying ages of onset. Breed-specific, population-based screening will help to control the incidence of inherited diseases in dogs, theoretically increasing the overall lifespan of a breed and reducing the costs associated with the care of a dog with a genetic disorder.

For any carrier screening program to be successful, laboratories should establish rigorous quality assurance programs that include critical review of the available literature on specific inherited diseases, the establishment and implementation of stringent validation protocols and procedures and on-going quality assurance plan to minimize sample mix-up and other laboratory errors. Finally, partnerships between the laboratory and breed clubs can help establish superior breeding programs that meet the needs of the breeders and positively impact the overall health of the breed.

CONFLICT OF INTEREST

CJR is an employee of Paw Print Genetics and serves as its medical director. LGS is owner of Paw Print Genetics, which provides carrier screening for inherited disorders to breeders, owners and veterinarians.

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