

Breeding Strategies for the Management of Genetic Disorders

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With each new generation, breeders ask, "How can I continue my line and improve it?" Aside from selecting for conformation, behavior and general health, breeders must consider how they are going to reduce the incidence of whichever genetic disorders are present in their breed. There are no answers that will fit every situation. There are, however, guidelines to preserve breeding lines and genetic diversity while reducing the risk of producing animals that carry defective genes, or are affected with genetic defects.

Autosomal Recessive Disorders

In the case of a simple autosomal recessive disorder (in other words, a disorder caused by a single, recessive gene that is not sex-linked) for which a test for carriers is available, the recommendation is to test your breeding-quality stock, and breed carriers to normal-testing animals. The aim is to replace the carrier breeding-animal with a normal-testing offspring that equals or exceeds it in quality. You don't want to diminish breed diversity by eliminating quality animals from the gene pool because they are carriers. As each breeder tests and replaces carrier animals with normal-testing animals, the problem for the breed as a whole diminishes.

In the future, some disorders may have linkage-based carrier tests, which can generate a small percentage of false positive and negative results. When using these tests to make breeding decisions, it's advisable to first determine whether the results correlate with test results and the known genotypes of relatives.

When dealing with a simple autosomal recessive disorder for which no carrier test exists, breeders must assess whether each individual animal in their breeding program is at high risk of being a carrier. This requires knowledge of the carrier or affected status of close relatives in the pedigree. An open health registry that is supported by the breed association makes it easier for breeders to objectively assess these matters. By determining the average carrier-risk for the breeding population, breeders can select matings that have a projected risk that is lower than the breed average.

If breeding an animal that is at high risk of being a carrier, the best advice is to breed to an individual that has a low risk. This will significantly diminish the likelihood that affected animals will be produced, and can reduce by up to half the risk that there will be carriers among the offspring. Using relative-risk assessment as a tool, breeders should replace higher-risk breeding animals with lower-risk offspring that are equal to or better than their

parents in quality. Relative-risk assessment allows for the continuation of lines that might otherwise be abandoned due to high carrier risk.

Breeding an individual only once and replacing it with an offspring allows breeders to improve their chances of moving away from defective genes and also limits the dissemination of defective genes. When dealing with disorders for which carriers cannot be identified, the number of offspring placed in breeding homes should be kept to a minimum.

Autosomal Dominant Disorders

Autosomal dominant genetic disorders are usually easy to manage. Each affected animal has at least one affected parent, but it can be expected that half of the offspring of an affected animal will be free of the defective gene. With disorders that cause death or discomfort, the recommendation is to not breed affected animals. To produce the next generation of a line, a normal full sibling of an affected animal can be used, or the parent that is normal can be used.

If the defective gene is at a high frequency in the gene pool, eliminating all affected breeding animals in one generation may have a significant negative impact on genetic diversity. In this case, some quality, affected animals may have to be bred, and replaced with quality, normal testing offspring.

A problem with some autosomal dominant disorders is incomplete penetrance, where some animals with the defective gene may not show the disorder. Roughly half their offspring, however, may be affected. If a genetic test is available, this is not a problem. Otherwise, relative-risk assessment can identify which animals are at risk of carrying incompletely penetrant dominant genes.

Sex-Linked Disorders

For sex-linked (also known as x-linked) recessive defective genes for which carrier tests exist, breeders should follow the same "breed and replace" recommendations as are outlined above in the discussion of autosomal recessive disorders. If there is no test, the defective gene can be traced through the pedigree. If a male is affected, he would have received the defective gene from his carrier mother. All of his daughters will be carriers, but none of his sons. By using relative-risk assessment to breed him to a female that is at low risk of being a carrier, you can prevent affected offspring, and select a quality son for replacement.

There are rare instances in which a female is affected with a sex-linked disorder. In such cases, she would have received the defective gene from both parents; specifically, an affected father and a mother who is either a carrier or is affected herself. If an affected

female is bred, all the sons will be affected, and all the daughters would be carriers, so affected females clearly should not be bred. A normal male that is a littermate to an affected female, however, would be able to carry on the line without propagating the defective gene.

Sex-linked dominant disorders are managed the same way as autosomal dominant disorders are. The difference is that affected males will **always** produce all affected daughters.

Polygenic disorders

Polygenic disorders are those caused by more than one pair of genes. Most polygenic disorders have no tests for carriers, but have phenotypic tests that can identify affected individuals.

With polygenic disorders, a number of genes must combine to cross a threshold and produce an affected individual. These are known as **liability genes**. In identifying an individual's liability for carrying defective genes for a polygenic disorder, the breadth of the pedigree (that is, consideration of all siblings of individuals in the pedigree) is more important than the depth of the pedigree (consideration only of parent-offspring relationships). A clinically normal Maine Coon cat from a litter that had no cats affected with hip dysplasia (which is a polygenic disorder) is expected to carry a lower amount of liability genes than a cat with a number of affected littermates. This is why it is important to screen both pet and breeding animals from your litters for polygenic disorders. Information on the siblings of the parents of potential breeding animals provides additional data on which to base your breeding decisions.

Genetic disorders without a known mode of inheritance should be managed like polygenic disorders. If there are multiple generations of normalcy in the breadth of the pedigree, then you can have some confidence that there is less risk that liability genes are being carried. If an individual is diagnosed with a genetic disorder, it can be replaced with a normal sibling or parent and bred to a mate whose risk of having liability genes is low. Replace the higher-risk parent with a lower-risk offspring that equals or exceeds it in other aspects, and repeat the process.

Genetic tests are extremely useful tools to help manage genetic disorders. Even when there is no test, or a known mode of inheritance, much can still be done to reduce the incidence of affected and carrier animals. The use of these guidelines can assist breeders in making objective breeding decisions for genetic-disease management, while continuing their breeding lines.