Practical clinical genetics

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Abstract

There is increasing evidence that many forms of congenital and acquired disease in veterinary medicine are of a familial origin. A veterinary practioner may be consulted on genetic issues of breeding animals to assist in breeding decisions and to provide pet owners information regarding etiology of diseases. Knowledge of mode of inheritance of a disease and information on possible genetic markers will help the practioner to arrive at recommendations for an individual animal and for breeding.

Keywords: Genetics, mutation, inherited, breeding

Introduction

There is increasing evidence that several forms of congenital and acquired disease in veterinary medicine are of familial origin. As of 2005, 430 canine diseases and 180 feline diseases had been identified as familial. It has been estimated that 5 - 10 new familial diseases are identified every year. Many familial veterinary diseases are assumed to be associated with improved control of diseases caused by environmental factors and the desire to breed animals to maintain an appearance, and selecting animals from a small group of popular founders (founder effect). It is reasonable to consider a familial etiology for common feline and canine heart diseases, particularly those with strong breed predispositions.

Many forms of congenital and acquired disease have a strong breed predisposition suggesting a familial etiology. A small animal practioner may be requested to provide consultation on genetic issues to provide information to owners of breeding animals to aid them in breeding decisions and to provide pet owners about etiologies of disease. Breed specific lists of known and presumed inherited diseases for dogs and cats are available at the following web sites:

Cats: http://www.fabcats.org/breeders/inherited_disorders/index.php

Dogs: http://www.vet.cam.ac.uk/idid/ and http://www.upei.ca/~cidd/intro.htm

Although the number of genetic diseases in small animals is substantial, the actual genetic cause is not commonly known. Even in the absence of knowledge of a molecular cause substantial amount of information can be provided from understanding the pattern of inheritance.

Genetic diseases are most commonly observed in purebred animals. Breed organizations have intentionally limited their gene pool by preventing breeding to other breeds. Therefore, the gene pool is limited and closed size, and aggressive removal of breeding animals because of the identification of a defect will make the gene pool even smaller. Consequently, one must CAREFULLY recommend removal of breeding animals based on severity of defect, mode of inheritance, and importance of a particular animal to the breed.

Genetic mutations rarely have an all or nothing effect. For some diseases, a genetic cause has now been identified and a genetic test can be done. Presence of the mutation does NOT mean that all animals will exhibit the trait, or similar severity of the trait; this depends on disease 'penetrance,' a poorly understood phenomenon that likely involves genetic modifiers.

Modes of inheritance

Knowledge on the mode of inheritance of a specific trait can be used to provide guidance about reducing the prevalence of a trait within a particular line of animals. Determination of the pattern of inheritance will be useful for determining the best recommendations for breeders and will allow development of plans to exclude or include affected animals in breeding programs. Common conditions include autosomal recessive, autosomal dominant, X-linked recessive, and X-linked dominant.

X-linked

X-linked traits are almost always recessive and should have the following criteria: more affected males than females, an affected male crossed with a normal (noncarrier) female should produce silent carriers, silent carrier females should have a 50:50 chance of passing the trait on to male offspring, and

affected females are the result of a cross between a silent carrier female and an affected male (not a frequent occurrence).

Example: Progressive retinal atrophy in the Akita.

Recommendation: If animals with an X-linked trait are used for breeding, they should always be bred to an unrelated line, as this will decrease the presence of the trait in the line.

Autosomal recessive

Autosomal recessive traits should have the following criteria: disease should appear to 'skip' a generation (parents do not usually exhibit the trait), males and females should equally exhibit the trait, the mating of 2 silent carriers (heterozygotes, carry 1 copy of the abnormal gene) should produce offspring that exhibit the trait in a 3:1 ratio, and if both parents exhibit the trait, all offspring should exhibit the trait.

Example: Diabetes mellitus in Keeshond

Recommendation: If animals with an autosomal recessive trait are used for breeding, they should always be bred to an unrelated line, as this will decrease the presence of the trait in the line.

Autosomal dominant

Autosomal dominant traits should have the following criteria: males and females should equally exhibit the trait, every affected individual should have at least 1 affected parent, and all heterozygotes (1 copy of the abnormal gene) are affected and transmit a mutant gene to half of their offspring. Affected animals may carry the genetic mutation on 1 or both copies of the gene. If it is on both copies of the gene (1 inherited from each parent) they are considered homozygous for the mutation and will pass 1 copy of the mutation to every offspring.

Example: Dilated cardiomyopathy in Doberman pinscher

Recommendation: If animals with an autosomal dominant trait are used for breeding, they have a 50 - 100% chance of passing on the trait (depending on if they are heterozygous or homozygous for the trait). Therefore, only those with the mildest form of the disease and the most positive attributes should be selected for use.

Utilization of molecular information for screening and therapeutic issues

In some cases, a molecular genetic cause for a specific trait has been identified and a genetic test is available. Genetic tests are generally a PCR test that identifies either a marker for the disease or identifies the actual genetic mutation. For PCR, a small DNA sample is provided by the clinician or owner and a region of interest is amplified so it can be carefully inspected. The DNA is usually provided in a blood sample in an EDTA tube, a buccal swab or even a semen sample. The DNA is inspected for the abnormality by the laboratory and for the presence or absence of the marker or mutation. However, breeders and owners should be cautioned and advised how to best use the information. Results should be carefully considered and should be weighed against the severity of the trait, the size of the breed's gene pool, the mode of inheritance of the trait and the positive traits that this individual animal brings to a breed. In some cases, strict screening and removal programs may be very detrimental to small gene pools in specific breeds; therefore, breeding recommendations should be carefully designed.

General guidelines for counseling owners about genetic diseases.

Genetic test results

Negative/wildtype: This indicates that the individual animal does not carry any copies of the known disease genetic variant (mutation).

Considerations for the individual animal and breeding population: No special considerations, since this animal should neither develop the inherited disease nor have the ability to spread disease within the population.

Positive heterozygous: This indicates that the animal has 1 copy of the normal gene (wild type) and 1 copy of the disease genetic variant.

Considerations for the individual animal: If the disease is autosomal recessive, this animal should never develop the inherited disease, so no special considerations are needed. However, if the disease is autosomal dominant, this animal is at risk of developing disease. Since this animal carries the disease variant and is at risk of disease development, a patient management strategy that includes annual monitoring for signs of disease and considers dietary, medical or other options. If the disease is X- linked recessive, a male with the disease variant on his X chromosome is likely to develop disease, whereas a female with the disease variant on 1 X chromosome is likely to be a silent carrier.

Considerations for breeding: If autosomal recessive, this animal will not develop disease and can be bred to an animal that is negative. This strategy will likely produce both negative and positive heterozygous animals but neither will develop disease. If the disease is autosomal dominant, a similar strategy for breeding could be considered and one could breed a positive heterozygous animal to a genotype negative animal. The offspring of this mating (positive heterozygous to a negative) will ideally produce at least some genotype negative offspring and 1 of these with the desirable traits of the parents could be selected to replace the positive heterozygous parent in future breedings. This breeding will also produce a few positive heterozygous animals. Hence this has a risk of producing animals that may suffer from disease. Therefore, this strategy should be considered with regard to the type of disease that may develop in the offspring. If the animal is exceptional due to personality, health, intelligence or other characteristics, one may more likely to try this approach once or twice in hopes of producing a genotype negative replacement animal. If the disease is X- linked recessive, a male with the mutation on the

X chromosome could be bred to a negative female. This will produce both male and females that do not have disease. The male offspring of this mating will not carry the mutation since males cannot pass on their X chromosome to their sons. Female offspring will also be clear of disease, they would need to carry it on both X chromosomes to actually demonstrate the disease. However, importantly, females with a disease variant on 1 X chromosome will be silent carriers of the trait.

Positive homozygous: This animal has 2 copies of the disease variant.

Considerations for the individual animal: Positive homozygous animals have the highest risk of developing the disease. A patient management strategy should be developed that may include annual monitoring for signs of disease and consideration to dietary, medical, or other options.

Recommendations for breeding animals: Since positive homozygous animals carry 2 copies of the mutation disease they will certainly pass on the mutation even when bred to a negative animal.

Finally, since these canine and feline familial diseases are complicated with issues that include incomplete penetrance, variable expression, closed gene pools and variable phenotypes. it is ideal to use a testing service that can provide the most expertise in genetic counseling for pet owners.