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Genetic diseases of cats

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In small animal practice, veterinarians are confronted by a bewildering number of disease conditions. As a generalisation, however, many disease conditions we see in dogs are ultimately genetic in aetiology, whereas most disease conditions in cats have a traumatic or infectious aetiology. This situation has arisen because a substantial proportion of dogs are purebreds or purebred-cross dogs. Breeding practices which have fixed a number of 'desirable' physical and behavioural traits have also established a number of genetic defects that ultimately give rise to disease. Some of these are obvious. Others, on the other hand, do not obviously make a veterinarian think of the underlying genetic predisposition.

By their very nature, some canine breeds are genetic mutants. Dachshunds and Bassets, for example, are obviously chondrodystrophic dwarfs. Toy poodles and Italian Greyhounds are midgets. Bulldogs have malformed heads which result in brachycephalic upper airway obstruction syndrome and fetal dystocia.

Other breeds have become very strongly associated with certain genetically inherited defects. For example, almost all Bedlington terriers (at least in Australia) have copper storage disease that ultimately gives rise to liver failure. There are other genetic diseases which are very common in certain breeds, such as the association between German Shepherds and hip dysplasia and Rottweilers and elbow dysplasia. Still other genetic diseases are not seen especially commonly, but have very strong breed associations, such as Yorkshire terriers and Maltese dogs with extrahepatic portosystemic shunts, Australian Cattle dogs and Irish Wolfhounds with intrahepatic portosystemic shunts and Border collies with patent ductus arteriosus, to give just a few examples. Some unfortunate breeds are predisposed to several genetically programmed diseases, which can occur in mix and match combinations. The Dobermann, for example, is a sad case, as individuals can suffer from dilated cardiomyopathy, Wobbler syndrome, Von Willebrand's disease and hypothyroidism.

But what is not well recognised by veterinarians is that a number of immune mediated and neoplastic diseases are likely also to be genetically programmed. Thus the predisposition to immune-mediated haemolytic anaemia, immune-mediated thrombocytopenia, aseptic suppurative meningitis (immune-mediated vasculitis) is genetic, as is the predilection to a number of neoplastic conditions (osteosarcoma, lymphoma, malignant histiocytosis). Indeed, it is fair to say that ultimately most disease conditions of purebred dogs have a genetic basis!

The situation in cats is different, in that historically cats have decided on their own sexual partners, at least in Australia! Thus, most cats we see as veterinarians are domestic crossbreds. For this reason, cats have been basically much more sound genetically in comparison to dogs. Thus, the diseases which we see commonly in domestic short haired and long haired cats tend to be related to trauma (vehicular trauma, dogs attack injuries, cat bite injuries) or infectious agents (herpesvirus, calicivirus, FIV, FeLV, FIP, feline

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infectious enteritis, feline infections anaemia, cat bite abscesses, pyothorax, cryptococcosis, mycobacteriosis etc). This state of affairs is likely to change as the population of crossbred cats declines as a result of cat registration, early desexing schemes, cat curfews and the like, and unfortunately if the proportion of purebred cats increases and current breeding practices prevail, then cats are at risk for developing the same high prevalence of genetically programmed diseases which currently afflict dogs.

This paper will focus on four genetic diseases of cats—osteochondrodysplasia of Scottish fold cats, polycystic kidney disease in Persian cats and muscular dystrophy and vitamin K-dependent coagulopathy in Devon Rex cats. These diseases are chosen to illustrate different types of genetic disease that may occur in purebred cat populations, and to highlight strategies that can be used to prevent or eliminate these problems.

Osteochondrodysplasia in Scottish Fold cats

The Scottish Fold cat was developed from a naturally occurring mutant cat that was first observed in a rugged part of Scotland in the early 1960s. The cat in which the mutant gene was first observed was used to 'fix' the trait by a number of restricted matings to local farm cats and British Shorthairs. Scottish Fold cats have as their defining feature a forward folding of the pinnae. This gives them a unique look, which many people find particularly appealing.

It was soon discovered, however, that if Scottish Fold cats were mated to other Scottish Fold cats, many of the offspring developed a crippling lameness early in life. Cats so affected had shortened, malformed legs and radiographic abnormalities affecting the growth plates. As a result of this discovery, the breed was outlawed by the Cat Fancy in the UK. Ironically, the breed was perpetuated in the United States, where breeders determined that offspring of matings of cats with folded ears to cats with normal ears were relatively normal, and that half of such matings (on average) had folded ears. In order to keep the type fixed, this practice was followed indefinitely; cats with the Scottish Fold type, but with normal ears, were thus produced in equal numbers from these matings. Such cats are known as Scottish Shorthairs or Scottish Fold variants.

Recent work conducted in Australia has confirmed earlier work that the cartilage defect that causes the ears of these cats to fold is transmitted as an autosomal dominant trait, but established for the first time that heterozygous Scottish Fold cats invariably become afflicted by a progressive arthritis that varies in severity from Fold to Fold. Thus cats homozygous for the Fold gene develop crippling arthritis at an early age, whereas heterozygous Folds develop arthritis but more slowly.

The cartilage in these cat's ears is insufficiently resilient to maintain the normal shape of the pinna, so it is hardly surprising that articular cartilage cannot cope with the wear and tear of a typical cat's agile and athletic lifestyle.

Thus, the problem with Scottish Fold cats is akin to that which affects many dog breeds which are genetic mutants. In other words, it is impossible to have a cat with Folded ears that has sound joints. The only answer to this problem would be to abandon the breeding of Folded eared cats. Breeders and owners who enjoy the particular personality of these cats could preserve them by having a Scottish Shorthair—a cat with the same body shape and personality, but without the defective gene that causes the cartilage problem. Whether breeders will accept this sensible solution is unknown.

Autosomal dominant polycystic kidney disease

PKD is an autosomally dominant disorder which is seen in all breeds of cats, but which has been reported with highest prevalence in Persian cats and related purebred, long haired cats. In this disease cysts develop in the renal cortex and medulla. Several theories have been put forward to explain the pathophysiology of cyst formation. As the cat grows older, cysts increase in size and number, and their growth results in compression of the surrounding 'normal' renal parenchyma. Eventually this results in renomegaly and progressive deterioration in renal function. The speed with this occurs varies a lot from cat to cat. Some cats can live near normal life spans, while others succumb to renal failure in middle age. The above description related to cats that are heterozygous for the defective gene. Cats that are homozygous are thought to either die in utero, or develop renal failure at a very early age.

PKD has been described in cats at least since the 1970s. Sometimes it is associated with the presence of cysts in the liver, and also with peritoneopericardial hernias. Recent work from Biller, DiBartola and collaborators has demonstrated convincingly that the disease is inherited

in an autosomally dominant fashion. Thus, all heterozygotes can be detected as they have cysts in their kidneys. Surveys of purebred long haired cats in several different countries have shown that approximately 40% of Persian and related purebred cats have PKD—just about what one would expect for a genetically transmitted autosomally dominant condition that has little impact on an individual till after it has passed breeding age.

The expression of the gene for PKD has nothing to do with the brachycephalic conformation of Persian cats, and as would be expected, we have traced the introduction of PKD into Burmilla cats, even though they have a normal facial conformation. Furthermore, PKD occurs sporadically in domestic cross bred cats, although it would appear to be more common in long haired cats, presumably as Persian blood lines were more prevalent in the ancestry of these individuals.

PKD has recently received a lot of attention from Persian breeders, partly as a result of Internet web sites alerting them to the importance and high prevalence of this condition. As a result many breeders have worked with cooperating veterinarians to screen their stock for PKD-positive cats in an attempt to eliminate this problem. Based on the experimental work of Biller, most cats with PKD can be identified at about 6 months of age using good quality ultrasound units and high frequency (7.5 to 10 MHz) transducers. The author prefers to screen cats somewhat later, around 12 months of age, as this makes the detection of mildly affected individuals much easier.

Theoretically, if all purebred long-haired cats were screened using ultrasonography, and PKD-positive individuals identified (usually on the basis of having three cysts in two kidneys; however recent work indicates that some cats with PKD initially can have just one large cyst in one kidney), then it should be possible to eliminate this problem from cats in one generation by desexing all affected individuals. A similar scheme used in Australia to eliminate ADPKD from Bull terriers has been remarkably successful at decreasing the prevalence of this condition, although this has required the concerted effort of many individuals breeders, breed clubs and veterinarians.

It should be mentioned, however, that although the simplest way to eliminate PKD is to cull all affected individuals, it is not necessary to immediately remove absolutely all affected individuals from breeding stock. If a particular cat with PKD is otherwise of outstanding quality (genotypically and phenotypically), it is still possible to use the cat for breeding with the proviso that all resulting progeny be screened for PKD, and affected individuals desexed. Thus the valuable genetic material in an individual cat can be preserved. This type of strategy is only practical with a autosomal dominant trait, where heterozygous carriers can be identified readily using ultrasonography.

Much research effort is being expended to precisely define the underlying genetic defect in affected cats. This would enable the genotype of a given cat to be determined at an early age using a DNA test on whole blood. This would avoid some of the controversy encountered using ultrasound to determine the status of a particular individual at a given point in time.

Autosomal recessive problems in Devon Rex cats

Devon Rex cats are an enchanting breed which have as their defining feature an autosomally recessive defect of the hair follicle. This defect results in the characteristic soft and crinkly hair coat of Devons. All Devon Rex cats are homozygous for the gene that results in their peculiar hair coat—so what you have is a mutant cat to start off with!

Two important autosomally recessive conditions have been reported in Devon Rex cats. 'Spasticity' as it is known to breeders, refers to a congenital myopathy somewhat similar to the human condition limb girdle muscular dystrophy. Work done in the UK established that the condition was inherited in an autosomal recessive fashion with complete penetrance. Affected cats usually show obvious signs of a locomotor problem when six to 20 weeks of age. Muscle weakness is the predominant feature, with prominent ventroflexion of the head and neck, dorsal protrusion of the scapulae, head bobbing, megaoesophagus and pharyngeal weakness. Affected cats have a generally unsatisfactory quality of life and are at risk of sudden death due to obstruction of the pharynx/larynx with food. Studies have shown the underlying problem to be a primary muscle disorder, although the molecular basis of the condition has not yet been determined.

There is no problem in diagnosing affected cats. Once a veterinarian (or breeder) is familiar

with the syndrome, the condition can be diagnosed on the basis of characteristic clinical signs, a barium swallow and biopsy of the dorsal cervical muscles (although there is really no need for the latter two diagnostic procedures in a characteristically affected kitten). The problem for the breed is how to eliminate this problem, when a molecular genetic test on blood is unavailable to detect heterozygous carriers.

The simplest approach is to stop using the queen and stud of affected cats for future breeding. This is because to produce an affected kitten, both sire and dam must be carriers (they can not be homozygous as they are phenotypically normal). A more aggressive approach would be to exclude the littermates of the sire and dam also from further breeding. Theoretically, the best approach would be to use only cats shown to be clear of the defective gene by test mating. Test mating involves breeding a cat of unknown genotype to a known carrier or carriers. If such matings result in the production of 16 normal kittens, statistics suggest the cat is normal, ie it does not have a copy of the defective recessive gene. The trouble with a test mating scheme is that in order to show that the given cat is clear, many carrier cats have to be produced, and thus these animals must be desexed and rehoused as pets. For practical reasons, most breeders are not keen on embarking on a test mating scheme, so the recommendation of not using the stud and queen that have produced an affected kitten is a pragmatic approach. In the future research may identify a molecular genetic test that will identify both homozygous affected cats and heterozygous carriers, which will greatly simplify the elimination of this problem.

'Spasticity' is so characteristic in its clinical manifestations that breeders have become adept at identifying affected individuals before kittens reach an age when they are sold and rehoused. The benefit of this is that it is most unlikely that an affected kitten will ever be sold as a pet. The disadvantage is that affected kittens may still be being produced, and subjected to euthanasia without the problem of eliminating the defective genes ever being addressed. There is, however, a much greater problem with another autosomally recessive condition of Devon Rex cats, known as 'hemophilia' to many breeders. The underlying problem is gamma-carboxylase deficiency, which results in a vitamin K-dependent coagulopathy (as gamma-carboxylase is involved in reconstituting vitamin K through the vitamin K cycle in the liver). Cats with this condition develop problems referable to abnormal coagulation, typically when less than one year-of-age. They may bleed excessively following trauma or minor surgery, eg, castration. They can also bleed spontaneously into the mediastinum and/or chest, and I have also seen one likely case where a kitten died of intracranial haemorrhage suspected of being caused by this condition. The tentative diagnosis can be confirmed by showing prolongation of the prothrombin time and activated partial thromboplastin time. These changes occur as there is deficiency of the vitamin K-dependent clotting factors (II, VII, IX and X)—so both the intrinsic and extrinsic pathways are affected. Cats experiencing a life-threatening bleeding episode should be treated with typed blood (mindful of the high prevalence of type B in Devon Rex cats) and subcutaneous vitamin K1, and further bleeding episodes can be prevented by weekly administration of vitamin K1 (one tablet of Konakion once a week).

Although the mechanism of genetic transmission has not been established beyond doubt, an autosomal recessive inheritance seems likely on the basis of analyses of pedigrees from affected individuals on record. However unlike congenital muscular dystrophy, affected individuals may not be apparent to the breeder, with the problem only emerging some time after the cat has been sold and placed in a pet home. Similar considerations apply to the elimination of this problem from the breed, although there is the additional problem of identifying homozygous individuals—as kittens have to be screened by determining their PTT and APTT to determine their phenotypic status. Unfortunately, very few breeders appear interested in screening kittens in this fashion prior to sale. As the underlying biochemical problem has been identified, there is the hope that a DNA test will be developed to identify heterozygous individuals, although considering the rarity of the breed this seems unlikely at present.

Concluding comments

This paper has served to illustrate the problems that can occur when small gene pools are used by well-meaning breeders that do not have a good understanding of genetics. Small animal veterinarians have an important role in educating breeders and the wider cat-owning community about how prevalent these disease conditions can become if inbreeding and line breeding are used. It is the authors firm opinion

that the purposeful breeding of domestic short haired cats to produce heathy cross bred kittens with hybrid vigour is the best way to prevent cats developing the high prevalence of genetic diseases which pervade purebred dogs. This will pose more of a challenge as the proportion of sexually intact cats declines in some countries due to early neutering and related strategies.

Further reading

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