Top 5 Genetic Diseases of Cats

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Most feline patients are random-bred domestic cats; random breeding propagates and disperses evolutionarily ancient disease-liability genes, which causes the random development of clinical genetic disease. Pedigreed breeds may have varied incidence of disease, depending on the frequencies of liability genes in their gene pools. Insurance claims and centralized hospital databases monitor the most frequent disease presentations, which helps veterinarians understand the most frequent genetic diseases. The most frequent conditions are complexly inherited and involve combinations of multiple genes and environmental factors. Genetic diseases should be recognized in practice because they must be treated as chronic illnesses—not episodic diseases.

1. Feline Lower Urinary Tract Disease (FLUTD)
Sterile FLUTD, including both feline idiopathic cystitis and feline urologic syndrome, is the most frequent feline hereditary predisposition observed in practice, affecting 1% to 2% of domestic cats. No infectious causes for FLUTD have been identified, and it can occur in individual cats in multicat households. Persian cats may be at increased risk, and Siamese cats may be at decreased risk for developing FLUTD. In an experimental model, when exposed to stressors, only cats predisposed to FLUTD developed clinical signs and showed mRNA responses for biomarkers vs controls. Similar gene-expression profiles are found in interstitial cystitis or bladder pain syndrome in humans, and a hereditary component has been documented. There is no

TOP 5 GENETIC DISEASES OF CATS
1. Feline Lower Urinary Tract Disease
2. Diabetes Mellitus
3. Lymphocytic or Plasmacytic Inflammatory Disease
4. Polycystic Kidney Disease
5. Hypertrophic Cardiomyopathy
established mode of inheritance, and no predisposing genes have been identified in cats.

Most practitioners recognize that once diagnosed and controlled, signs associated with FLUTD can recur if owners are not diligent about controlling predisposing factors. Such measures can include minimizing environmental stress, maintaining anti-inflammatory or behavior-modifying drugs that decrease likelihood for bladder inflammation, and maintaining dietary control for cats predisposed to crystalluria.

2 Diabetes Mellitus
Diabetes mellitus is a common diagnosis in cats controlled via insulin regulation and diet.\textsuperscript{13} It is primarily seen in random-bred cats, although an increased incidence is seen in Burmese\textsuperscript{14} and possibly Siamese, Norwegian forest, Russian blue, and Abyssinian cats.\textsuperscript{15,16} Obesity is a predisposing factor.\textsuperscript{17} One study found a mutation in the melanocortin 4 receptor gene to be significantly associated with diabetes in obese domestic shorthair cats.\textsuperscript{17} This is similar to findings associated with human type 2 diabetes.\textsuperscript{17}

3 Lymphocytic or Plasmacytic Inflammatory Disease
Predisposition toward lymphocytic or plasmacytic inflammation represents a complex immunologic response involving innate, humoral, and cell-mediated immunity. In cats, lymphocytic or plasmacytic inflammatory disease most frequently manifests as gingivostomatitis\textsuperscript{18} or inflammatory bowel disease (IBD).\textsuperscript{19} Although the histopathologic descriptions of these 2 entities are similar, they rarely occur in the same patient.

Breed predisposition to IBD has been found in Siamese and other Asian breeds, but causal genetic mutations have not been found.\textsuperscript{19} Liability genes for IBD have been identified in German shepherd dogs\textsuperscript{20} and humans.\textsuperscript{21} Liability genes have been identified for recurrent aphthous stomatitis in humans, the corollary to feline lymphoplasmacytic gingivostomatitis.\textsuperscript{22}

Many possible environmental variables exist, including diet (and possibly dietary reactivity), reactivity to the local microbiome, and behavioral stress.\textsuperscript{6,20} Affected cats show a lifelong propensity to inflammatory cell infiltration that does not occur in other cats in the same household. Control of both conditions can include dietary changes, anti-inflammatory or immunoregulatory drugs, minimization of environmental stress, and dental extraction in cats with severe gingivostomatitis.

4 Polycystic Kidney Disease\textsuperscript{23}
Polycystic kidney disease (PKD) is the most common single-gene feline disorder seen in practice. It is caused by an autosomal dominant gene for which a commercial genetic test exists (UC-Davis VGL). This defective gene is present in 38% of Persian cats (6% of cats worldwide), as well as in high frequencies in Himalayan and other Persian-derived breeds. PKD is also seen in random-bred longhair cats with presumed Persian ancestry. All affected cats are heterozygous for the defective gene, as homozygosity is prenatally lethal.

Most affected cats develop kidney failure at an average age of 7 years (range, 4-10 years).\textsuperscript{24}

\textsuperscript{FLUTD = feline lower urinary tract disease, IBD = inflammatory bowel disease, PKD = polycystic kidney disease}
Variable expression of this gene can be noted in cats that develop a few cysts but maintain normal renal function. There is no specific treatment aside from support for chronic kidney disease and failure.

Prospective pet owners interested in kittens of susceptible breeds should ask for the PKD DNA test results on both parents and/or the kittens. Breeders who offer a breeding stock that is “PKD clear” on ultrasonography are using an outdated and unreliable diagnostic standard. If valid PKD DNA test results are not available from the breeding stock, potential pet owners can collect a cheek swab from kittens for testing.

**Hypertrophic Cardiomyopathy**

Hypertrophic cardiomyopathy (HCM) occurs as a breed-related disease in several breeds as well as in random-bred cats. A mutation in the myosin-binding protein C gene occurs in 33% of Maine coon cats and causes highly penetrant, autosomal-dominant HCM. Affected cats can experience heart failure or sudden death at 6 months to 7 years of age. Cats homozygous for the mutation have a more severe and earlier-age onset than do heterozygotes. The disease shows incomplete penetrance, and some heterozygous cats can remain clinically normal.

Twenty percent of ragdoll cats carry a different mutation in the same gene that causes HCM. A genetic test is available for breed-specific mutations in the ragdoll and Maine coon breeds. Prospective breeding cats should be tested, or kittens should be tested before placement.

HCM also occurs in individual Maine coon and ragdoll cats not carrying the breed-specific mutations, as well as in random-bred cats and individual cats of other breeds. These findings support both within-breed and between-breed genetic heterogeneity for the disease. Clinical treatment for HCM involves controlling heart failure.

Cats of the sphynx breed may develop an earlier-age (average, 2 years) onset HCM. In Norwegian forest cats, cardiomyopathy with signs of both hypertrophic and restrictive disease has been documented. HCM has also been reported in Persian, Chartreux, Bengal, and Birman cats. Causative genes have not been identified in these breeds, but pedigree studies suggest dominant inheritance with incomplete penetrance.

**Conclusion**

Other common feline diseases with hereditary components include calcium oxalate bladder stones, allergic skin disease with or without eosinophilic granuloma complex, mammary tumors, and lymphoma. Hyperthyroidism is frequently seen in practice, but the cause is thought to be related to environmental goitrogen and not heredity. There is also no published evidence for heritability of chronic kidney disease seen in older cats.

Many breed-specific genetic diseases are seen at a lower frequency in clinical practice. The WSAVA Canine and Feline Hereditary Disease (DNA) Testing website (research.vet.upenn.edu/WSAVA-LabSearch) is an excellent source of information on DNA tests, susceptible breeds, and testing laboratories.

Cats affected with genetic disorders should not be used for breeding. For complexly inherited genetic disorders, risk for carrying disease-liability genes should be based on knowledge of clinical disease or normalcy in first-degree relatives of prospective breeding cats. Carriers of testable recessive disease-liability genes can be bred with normal-testing mates and replaced for breeding with normal-testing offspring. Cats with testable dominant disease-liability genes should be replaced for breeding with normal-testing relatives.

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References

**Bayer**

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Genetic diseases, common in crossbreed and purebred dogs, are typically associated with evolutionarily ancient disease-liability genes that preceded the separation of breeds and are dispersed in the domestic dog genome. In the past century, the most common diseases in dogs have resulted from infectious, nutritional, and environmental causes. As clinicians have learned to manage the causes of these diseases (eg, through vaccination and proper diet), genetic predisposition has become a more frequent etiology of disease. Frequency of common genetic disorders varies among breeds and may be caused by random changes (ie, genetic drift), popular sire syndrome, selection for aesthetic traits linked on chromosomes to disease-liability genes, or anatomic or conformational aspects that can alter disease liability.

The hallmark of inherited disease is predictability of onset and progression. Recognizing predictable triggers and modifying factors that influence the expression of genetic disorders can help improve diagnosis, treatment, and control.
1 **Allergic Skin Disease**

According to insurance claims and centralized hospital databases, allergic skin disease manifestations (e.g., chronic inflammatory otitis, recurrent hot spots) are the most frequent disease presentations in clinical practice.\(^2\)-\(^5\) These presentations are commonly seen in crossbreed and purebred dogs; some breeds have a higher incidence than others.\(^6\)-\(^8\) A study of atopic dermatitis in golden and Labrador retrievers showed heritability (i.e., percent of liability due to genetic influence) at 47%, which indicates a significant environmental contribution.\(^9\)

A molecular genetic study of atopic dermatitis in German shepherd dogs identified an associated segment of chromosome 28.\(^10\)

No genetic-liability tests are available. Predictable seasonality can be recognized in 15% to 62% (median, 30%) of allergic dogs with chronic presentations.\(^7\) For these patients, interventional measures to manage pruritus should be prescribed before it progresses to clinical disease.

2 **Canine Hip Dysplasia**

Hip dysplasia, which occurs across all crossbreed and purebred dogs, is the most common inherited musculoskeletal disorder.\(^11\) Of all dogs for which radiographs are submitted to the Orthopedic Foundation for Animals (ofa.org), 14.59% are rated as dysplastic. This is likely a low estimate, as clinically apparent cases may not be submitted for evaluation.\(^11\) Small dogs with hip dysplasia usually do not show the pain and discomfort seen in larger dogs; this demonstrates a size–weight relationship to clinical presentation.\(^12\) Radiographic diagnosis is made through ventrodorsal view or distraction index.\(^12\)

Palpable hip laxity can predict hip dysplasia and later osteoarthritic changes.\(^13\) A gentle Ortolani procedure during puppy examination and palpation for hip laxity under anesthesia during neutering should be performed. Dogs with severe laxity identified at an early age may benefit from interventional surgery.\(^12\)

Estimated breeding values and genotypic breeding values based on DNA marker panels are being experimentally developed to assist with selection for hip normalcy.\(^14\) Breeders should select for familial breadth and depth of normalcy as seen in vertical pedigrees.\(^15\)

3 **Brachycephalic Obstructive Airway Syndrome**

Brachycephalic obstructive airway syndrome (BOAS) is a disorder of breathing difficulty in short-snouted and “bully” breeds.\(^16\) Breeds with the highest prevalence include bulldogs, French bulldogs, and pugs.\(^17\) BOAS occurs because of a mismatch in the proportions of the skull and soft tissue in the nose and pharynx. Clinical signs include dyspnea, exercise intolerance, heat intolerance, abnormal and increased respiratory noise, cyanosis, syncope, and death.\(^18\) In one study, 16.7% of high-risk dogs died of respiratory failure at an average of 8.6 years of age.\(^19\)

This syndrome includes stenotic nares, an elongated soft palate, everted laryngeal sacs, laryngeal collapse, and/or a hypoplastic trachea.\(^16\) Brachycephalic dogs may be presented with facial skin fold dermatitis and corneal ulceration. For dogs experiencing significant morbidity, corrective surgery can include rhinoplasty for stenotic nares, soft palate resection, and laryngeal sacculle removal.\(^16,20\) Breeders should select for dogs that do not show signs of BOAS and that have a muzzle at least one-half the depth of the cranial length (from occiput to the front of the cranium), a normal-diameter trachea (ratio of lumen diameter at the thoracic inlet to the width of the proximal third rib should be ≥2 on a lateral radiograph), and nostrils that are 33% the width of the nose.\(^18,20\)
4 Myxomatous Mitral Valve Disease

Myxomatous mitral valve disease (ie, mitral valve endocarditis) is primarily seen in toy breeds and small patients.\textsuperscript{21,22} For some breeds (eg, Norfolk terrier, Cavalier King Charles spaniel), it may lead to heart disease at an average age of 6.25 years.\textsuperscript{23} As this is beyond breeding age, some Cavalier King Charles spaniel clubs have established a generational breeding-control program in which dogs are only bred if both parents are free of a murmur and Doppler evidence of mitral regurgitation. When this program is applied, the frequency of this disorder has decreased.\textsuperscript{24}

5 Cranial Cruciate Ligament Rupture

Cranial cruciate ligament rupture is a common traumatic injury. Although it is not typically considered a hereditary disease, studies show increased risk in rottweilers, West Highland white terriers, golden retrievers, Yorkshire terriers, Staffordshire bull terriers, and some crossbreed dogs.\textsuperscript{1,25} Studies of cranial cruciate ligament rupture in Newfoundlands show 27% heritability.\textsuperscript{26,27} Genetic predisposing factors for rupture may include issues with ligament extracellular matrix metabolism, degeneration, and/or inflammation. Other predisposing factors may also involve biomechanical and conformational variations (eg, bone length, stifle angulation, tibial plateau variation, narrowed distal femoral intercondylar notch).\textsuperscript{28}

Conclusion

The WSAVA Canine and Feline Hereditary Disease (DNA) Testing website (research.vet.upenn.edu/WSAVA-Lab Search) is an excellent source for DNA tests, lists of susceptible breeds, and testing laboratories.\textsuperscript{29}

Dogs affected by genetic disorders should not be selected for breeding. Because most of these genetic diseases are complexly inherited, genetic risk for carrying disease-liability genes should be based on knowledge of clinical disease or normalcy in first-degree relatives of prospective breeding dogs.

OTHER COMMON CANINE GENETIC DISEASES\textsuperscript{1-6}

- Patella luxation
- Autoimmune thyroiditis
- Cancer predisposition (lymphoma, hemangiosarcoma, mast cell tumor, osteosarcoma)
- Hereditary cataracts
- Nonstruvite bladder stones
- Elbow dysplasia
- Cryptorchidism
- Hepatic shunts
- Epilepsy
- Glaucoma
- Deafness
- Blindness
- Renal dysplasia
- Addison disease

IDENTIFIED MENDELIAN LIABILITY GENES: COMMON DISORDERS\textsuperscript{30}

- Arrhythmogenic right ventricular cardiomyopathy (boxers, boxer crossbreeds)
- \textit{MDRI}-related ivermectin and drug sensitivity
- Lens luxation
- Degenerative myelopathy
- von Willebrand disease
- Progressive rod-cone degeneration form of progressive retinal atrophy
References