

Genetics of Feline Diseases and Traits

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The inherited diseases and traits currently described in the cat are more likely to be identified in a specific breed than in random-bred cats. More than 88 million owned cats are estimated in the United States.² Only a small percentage of this cat population is represented by cats of a specific breed, perhaps at most 15%.⁶³ Many traits that can also be considered diseases are actually the hallmarks or identifiers of some cat breeds. Inbreeding does not cause mutations to occur at a higher rate within a breed, although inbreeding, popular sire effects, and population bottlenecks will allow rare mutations to occur more frequently within the population. Usually, recessive mutations, which can go unrecognized for many generations because they require the causative mutation to be present on both chromosomes, are the traits and diseases that tend to suddenly appear in inbred populations. The higher likelihood of an undesired trait appearing in a breed population gives the impression that breeds are unhealthier than random-bred populations. Fortuitous and deleterious mutations occur at the same rate in cats, regardless of whether the cat is pedigreed or random bred. Fancy-breed cats are more likely to have a higher standard of health care and are more likely to be closely observed than the random-bred alley cat or housecat. Thus ascertainment bias contributes to the identification of deleterious traits that are presented to the veterinarian. However, many mutations have been found in random-bred domestic shorthairs. This chapter reviews the known inherited diseases of the cat from the genetic point of view. Additional details regarding the diagnosis and treatment of the specific diseases can be found in other chapters in this volume. A list of common genetic terms can be found in **Box 44-1**.

Diseases or conditions that are caused by genetic abnormalities cannot be cured, but the associated health problems may be manageable. An overall goal for identifying the genetic mutations for genetic conditions is the correction of the defect by way of gene or stem cell therapies or better management by way of designer drug therapies. Genetic testing is currently an effective preventive medicine because proper breeding can prevent the birth of diseased individuals; moreover, genetic testing may lead to the potential ultimate cure.

HALLMARKS OF GENETIC DISEASES

A cat's appearance, its phenotype, is a combination of visible traits and morphologic types. Attributes of the phenotype can be desirable or undesirable. As in breeds of other species, a disease or health concern can sometimes be considered part of the cat's desired phenotype. For example, a Manx cat is tailless, but incontinence and lameness are associated with the characteristic of having no tail. Because phenotypes can be a result of a single gene, the interaction of several genes, the accumulation of environmental exposures, or a combination of interactions, a veterinarian may choose different types of therapy or clinical management or make different prognoses if a phenotype is known to have mainly a genetic cause. If the same condition is found in a different species, a veterinarian may have opportunities to try novel approaches for health care by considering comparative medicine. Several characteristics are common to genetic diseases that will help distinguish sporadic, idiopathic occurrences from inherited conditions.

BOX 44-1**Glossary of Genetic Terms**

Allele: Alternative form of a gene. One of the different forms of a gene that can exist at a single locus.

Base pair: The nucleotides that constitute a strand of DNA are also known as *bases*. A base pair implies the nucleotide from one strand of DNA and the pair with which it forms hydrogen bonds on the second strand of DNA, such as cytosine binding with guanine or adenine binding with thymine. The two strands of DNA are bound together by the hydrogen bonds of base pairs to form the double helix of DNA.

Common ancestry: The state of two individuals when they are blood relatives. When two parents have a common ancestor, their offspring will be inbred.

DNA (deoxyribonucleic acid): An antiparallel double helix of nucleotides (having deoxyribose as their sugars) linked by phosphodiester (sugar-phosphate) bonds to adjacent nucleotides in the same chain and by hydrogen bonds to complementary nucleotides in the opposite chain. The fundamental substance of which genes are composed.

Dominant allele: An allele that expresses its phenotypic effect even when heterozygous with a recessive allele; thus if A is dominant over a, then AA and Aa have the same phenotype.

Exon: A region of a gene that is present in the final functional transcript (mRNA) from that gene. Any non-intron section of the coding sequence of a gene; together the exons constitute the mRNA and are translated into protein.

Gene: Segregating and heritable determinant of the phenotype. The fundamental physical and functional unit of heredity, which carries information from one generation to the next. A segment of DNA, composed of a transcribed region and regulatory sequences that make possible transcription.

Gene interaction: The collaboration of several different genes in the production of one phenotypic character (or related group of characters).

Gene locus: The specific place on a chromosome where a gene is located.

Gene mutation: Mutation (point or larger change) that results from changes within the structure of a gene.

Genetic polymorphism: The occurrence together in the same population of more than one allele or genetic marker at the same locus with the least frequent allele or marker occurring more frequently than can be accounted for by mutation alone.

Genetic variance: Phenotypic variance resulting from the presence of different genotypes in the population.

Genetics: (1) The study of genes through their variation. (2) The study of inheritance.

Genome: The entire complement of genetic material in a chromosome set. The entire genetic complement of a prokaryote, virus, mitochondrion, or chloroplast or the haploid nuclear genetic complement of a eukaryotic species.

Genotype: The specific allelic composition of a cell, either of the entire cell or more commonly for a certain gene or a set of genes. The genes that an organism possesses.

Heritability: A measure of the degree to which the variance in the distribution of a phenotype is due to genetic causes. In the broad sense, it is measured by the total genetic variance divided by the total phenotypic variance. In the narrow sense, it is measured by the genetic variance due to additive genes divided by the total phenotypic variance.

Heterozygosity: A measure of the genetic variation in a population; with respect to one locus, stated as the frequency of heterozygotes for that locus.

Heterozygote: An individual having a heterozygous gene pair. A diploid or polyploid with different alleles at a particular locus.

Inbreeding: The mating of genetically related individuals. Mating between relatives.

Inbreeding depression: A depression of vigor or yield due to inbreeding.

Incomplete dominance: The situation in which both alleles of a heterozygote influence the phenotype. The phenotype is usually intermediate between the two homozygous phenotypes. The situation in which a heterozygote shows a phenotype somewhere (but not exactly halfway) intermediate between the corresponding homozygote phenotypes. (Exact intermediacy is not dominance.) See also dominance, co-dominance, and recessivity.

Intron (intervening sequence): A DNA segment of largely unknown function within a gene that specifically interrupts the coding (exon) sequences of that gene. Introns are transcribed as part of the normal gene primary transcript, but intron sequences are not found in the functional mRNA. Intron sequences are removed from the primary transcript by a splicing mechanism.

Locus (plural, loci): The position of a gene, DNA marker, or genetic marker on a chromosome.

Mosaic: A chimera; a tissue containing two or more genetically distinct cell types, or an individual composed of such tissues. Individual made up of two or more genetically distinct cell lines.

Mutant allele: An allele differing from the allele found in the standard or wild-type organism.

Mutation: (1) The process producing a gene or a chromosome differing from the wild-type. (2) The gene or chromosome that results from such a process.

Mutation rate: The number of mutation events per gene per unit of time (e.g., per cell generation). The proportion of mutations per cell division in bacteria or single-celled organisms or the proportion of mutations per gamete in higher organisms.

Nucleotide: One of four bases that constitute DNA, including adenine, guanine, cytosine, and thymine.

Pedigree: A family tree drawn with standard genetic symbols, showing inheritance patterns for specific

BOX 44-1**Glossary of Genetic Terms—cont'd**

- phenotypic characters.** A representation of the ancestry of an individual or family; a family tree.
- Penetrance:** The proportion of individuals with a specific genotype who manifest that genotype at the phenotype level.
- Phenocopy:** A phenotype that is not genetically controlled but looks like a genetically controlled phenotype. An environmentally induced phenotype that resembles the phenotype produced by a mutation.
- Phenotype:** (1) The form taken by some character (or group of characters) in a specific individual. (2) The detectable outward manifestations of a specific genotype. (3) The observable attributes of an organism.
- Pleiotropy:** The phenomenon whereby a single mutation affects several apparently unrelated aspects of the phenotype.
- Point mutation:** A mutation that can be mapped to one specific site within a locus. A small mutation that consists of the replacement (transition or transversion), addition, or deletion (frameshift) of one base.
- Popular sire:** A specific male in a population whose genetics becomes overrepresented in the next generation as a result of excessive breeding. Popular sires are determined by some quality desired in the population and generally represent high-winning individuals for a breed in competition. A undesired recessive trait can quickly spread in a population as a result of the popular sire effect.
- Recessive:** (1) An allele that is not expressed in the heterozygous condition. (2) The phenotype of the homozygote of a recessive allele.
- Selection:** Genetic breeding methods start with selecting particular desirable phenotypes as parents for the next generation.
- Sex chromosome:** A chromosome whose presence or absence is correlated with the sex of the bearer; a chromosome that plays a role in sex determination. Heteromorphic (different-shaped [e.g., X and Y]) chromosomes whose distribution in a zygote determines the sex of the organism.
- Sex linked:** The inheritance pattern of loci located on the sex chromosomes (usually the X chromosome in XY species); also refers to the loci themselves.
- Silent mutation:** Mutation in which the function of the protein product of the gene is unaltered.
- X chromosome inactivation:** In female mammalian embryos, the early random inactivation of the genes on one of the X chromosomes, leading to mosaicism for functions coded by heterozygous X-linked genes.

The following are six common hallmarks for inherited diseases:

1. Early age of onset
2. Bilateral or multiple presentation (or both)
3. Presence in a closed or small population
4. Indications of inbreeding
5. Uniformity in presentation
6. Advanced parental age at birth

Only advanced age of parents at birth has not been shown to have an effect in feline inherited diseases to date. Examples of parental age effects in humans include older or very young mothers having a higher frequency of children with trisomy 21 (Down syndrome)⁷⁷ and certain types of dwarfism being associated with advanced paternal age.⁷⁸

Two examples of diseases that present as sporadic and inherited forms are kidney cysts¹³ and lymphosarcoma.⁶³ Each of the five characteristics that define genetic diseases can help differentiate cats with polycystic kidney disease (PKD) from cats with sporadic kidney cysts. Kidney cysts can occur in any cat, but not all cystic presentations are indicative of PKD. PKD can sometimes be detected by ultrasound as early as 6 to 8 weeks of age, consistently by 10 months of age.²⁶ Both kidneys are generally affected, and multiple cysts are generally

present (see Figures 32-4 and 32-5). The cysts are not similar in size but are similar in etiology. PKD is rampant in Persian cats and therefore must be considered a health concern in related breeds, such as Exotic Shorthairs and Himalayans. Surprisingly, this genetic problem has a very high frequency in one of the oldest and largest cat breeds, which is not a small or closed population, but the early onset, the bilateral presentation, and the high prevalence in a breed clearly demarcate this condition as a heritable problem. An older, random-bred cat with one or a few cysts in one kidney would not be a candidate for heritable PKD and genetic testing.

Lymphosarcoma is also common in cats but generally found in older cats and cats that have been infected with feline leukemia virus (FeLV).³³ Mediastinal lymphosarcoma has been specifically identified in Oriental Shorthairs that are FeLV negative and generally younger than 2 years of age,^{31,32} although a genetic cause has not yet been identified. Other related breeds, such as Siamese, Colorpoint Shorthair, and the longhaired varieties of Siamese, have an increased prevalence of this type of lymphoma. The tumors respond well to chemotherapy, but reoccurrence is high, and the disease generally carries a very poor prognosis. This disease is found in a closed, inbred population; it has an early onset and a generally uniform presentation; and the tumor is found

in areas not common to older-onset forms of lymphosarcoma. These hallmarks strongly suggest that mediastinal lymphoma is a heritable condition in the Oriental cats.

Non-genetic components (e.g., toxins, infections, infestations, sporadic damage and changes to the DNA, and environmental influences such as diet, exercise, and social surroundings) can produce a phenotype that looks just like an inherited characteristic or disease; this is termed a *phenocopy*. Detailed examinations of cats with heart murmurs may reveal different presentations of heart disease, one that may be genetic and one that may be environmentally induced, such as by insufficient dietary taurine resulting in dilated cardiomyopathy.⁸² Some diseases may present differently in different tissues, which is termed *pleiotropic effects* of the same gene. For example, some completely white cats show only the white coat color; others have blue eyes or one blue and one green eye, and some may be deaf.^{4,10,99} The variations in eye color and hearing are pleiotropic effects of the *White* gene for cats. Genetic testing can help the clinician rule out the common and environmental causes of clinical presentations as opposed to a condition caused by a heritable defect in the cat's DNA.

SIMPLE GENETIC TRAITS

A cat's phenotype and its health can be influenced by both genetic (inherited) and nongenetic (environmental) influences. The diseases and traits that have known mutations—hence clearly heritable and genetic—are generally called *simple*, or *single, gene traits*, because the presentations are controlled mostly by a specific mutation in a specific gene. Environment may play some role in the overall presentation of a simple genetic trait, but the major contribution to the phenotype is from the single gene defect. Most of the early identified mutations for any species have been single gene traits, mainly because the presentation is similar to that found in another species. Comparative genetics and comparative medicine work in a similar fashion; the genetic knowledge for one species can be transferred to another species. Through comparative genetics genes that cause defects in one species, such as humans, dogs, or mice, can be scanned for causative mutations when a similar disease presentation or phenotype is discovered in the cat.

Genetic Traits with Known Mutations

The comparative genetics approach is also often termed a "candidate-gene" approach. Discovered in the early and mid-1990s, the first mutations identified in cats were for lipid and lysosomal storage diseases^{100,102} because these diseases have well-defined phenotypes and known genes with mutations that were as found in humans (see reviews by Banks and Chamberlain,⁶ and

Valayannopoulos et al¹⁹⁷). Most of the common diseases, coat colors, and coat types have been deciphered in the cat following the same candidate-gene approach, by finding a replicate trait in another species, usually mice, and checking the same gene for causative mutations.

Once a mutation is known, a genetic-based test can be established. DNA testing for domestic cat diseases and appearance traits is a rapidly growing asset for the veterinary community. Approximately 33 genes contain approximately 50 mutations that cause feline health problems or alterations in the cat's appearance (Tables 44-1 and 44-2). To date, other than the muscular dystrophy mutation,¹⁰⁰ all mutations in the cat are autosomal, not found on the X or Y chromosomes. A variety of commercial laboratories can now perform feline genetic diagnostics, allowing both the veterinary clinician and the private owner to obtain DNA test results. DNA is easily obtained from a cat by buccal swab using a standard cotton bud or cytologic brush, after which DNA samples can be sent to any laboratory in the world because the DNA is stable at room temperature. The DNA test results identify carriers of the traits, predict the incidence of traits in breeding programs, and influence medical prognoses and treatments. Once a genetic test proves that an animal has a genetic trait, preventive therapies and dietary restrictions could be implemented to slow or prevent the onset and progression of the associated disease. Thus genetic testing should not be viewed as an alternative to veterinary care but instead as a tool for veterinary care, part of a cat's overall health management plan.

Phenotypic Mutations of the Domestic Cat

Domestic cats have been selected to produce breeds mainly on the basis of aesthetic qualities, especially coloration, fur length and type, and some morphologic types such as folded or curled ears. Most of the genes controlling these traits are simple, and many of the causative mutations have been identified. Tables 44-1 and 44-3 present the common genes and loci that affect feline phenotypic traits. A trait is initially given a locus name, such as *Brown*, before the actual gene has been identified. The locus name usually is a descriptor of the trait, although the location in the genome for the locus will not be initially known; however, the mode of inheritance of the different alleles is usually determined. The alleles are given single- or two-letter designations, lower case implying a recessive allele. Once the gene is identified, such as *tyrosinase-related protein 1* (*TRYP1*) for *Brown*, the mutations are written to describe the genetic alteration within the gene, and the gene will be designated with the alleles, such as *TRYP1^b* for the brown allele.

Several of the cat coat color loci have only one mutant allele, such as *Agouti*, *Dilute*, and *Extension*. Because the phenotypic mutations are of value to cat breeders for

TABLE 44-1 Common Commercialized DNA Tests for Domestic Cats

Disease/Trait	MOI*	Phenotype	Breeds	Gene	Mutation
Agouti ²⁷	AR	Banded fur to solid	All breeds	<i>ASIP</i>	del122-123
Amber ⁸¹	AR	Brown color variant	Norwegian Forest	<i>MC1R</i>	G250A
Brown ^{65,90}	AR	Brown, light brown color variants	All breeds	<i>TYRP1</i>	b = -5IVS6, b ^l = C298T
Color ^{47,66,90}	AR	Burmese, Siamese color pattern, full albino	All breeds	<i>TYR</i>	c ^b = G715T, c ^s = G940A, c = C975del
Dilution ⁴⁸	AR	Black to gray/blue, orange to cream	All breeds	<i>MLPH</i>	T83del
Gloves ³⁴	AR	White feet	Birman	<i>KIT</i>	c.1035_1036delinsCA
Hairless (Naked) ³⁵	AR	Atrichia	Sphynx	<i>KRT71</i>	c.816_1G_A
Long fur ^{25,52}	AR	Long fur	All breeds [†]	<i>FGF5</i>	c.356insT, C406T, c.474delT, A475C
Rexing (curly fur) ³⁵	AR	Curly hair coat	Devon Rex	<i>KRT71</i>	c.1108-4_1184del, c.1184_1185insAGTTGGAG
AB blood type ¹¹	AR	Determines type B	All breeds	<i>CMAH</i>	18indel-53, G139A
Gangliosidosis 1 ²³	AR	Lipid storage disorder	Korat, Siamese	<i>GLB1</i>	G1457C
Gangliosidosis 2 ¹⁴	AR	Lipid storage disorder	Burmese	<i>HEXB</i>	15bp del (intron)
Gangliosidosis 2 ²⁶	AR	Lipid storage disorder	Korat	<i>HEXB</i>	C39del
Glycogen storage disease IV ^{28a,68}	AR	Glycogen storage disorder	Norwegian Forest	<i>GBE1</i>	230bp ins 5'-6kb del
Hypertrophic cardiomyopathy ⁷⁵	AD	Cardiac disease	Maine Coon	<i>MYBPC</i>	G93C
Hypertrophic cardiomyopathy ⁷⁴	AD	Cardiac disease	Ragdoll	<i>MYBPC</i>	C2460T
Progressive retinal atrophy ⁷²	AR	Late onset blindness	Abyssinian	<i>CEP290</i>	IVS50 + 9T > G
Progressive retinal atrophy ⁷³	AD	Early onset blindness	Abyssinian	<i>CRX</i>	n.546delC
Polycystic kidney disease ⁶⁴	AD	Kidney cysts	Persian	<i>PKD1</i>	C10063A
Pyruvate kinase deficiency [‡]	AR	Hemopathy	Abyssinian	<i>PKLR</i>	13bp del in exon 6
Spinal muscular atrophy ³⁰	AR	Muscular atrophy	Maine Coon	<i>LIX1-LNPEP</i>	140kb del, exons 4-6

AD, Autosomal dominant; AR, autosomal recessive; ID, incomplete dominance; AS, allelic series.

*Mode of inheritance of the non-wild-type variant.

†Long fur variants are more or less common depending on the breed.

‡Unpublished test, presented only as abstract.

managing their breeding programs, the phenotypic mutations generally have genetic tests readily available from commercial services. Because most of the mutations for the aesthetic traits are recessive, the mutant alleles must be present in both copies for the effect to be visible, and cats can carry the mutation without detection. Recessive mutations tend to be found in the genes that produce the enzymes of biological pathways. Thus most of the coat color mutations are recessive because they are usually part of disrupting the pigment production pathways. Many genes that affect pathways also tend to have more than one mutation that cause different effects; this is termed an *allelic series*. The locus for brown color variants, *Brown*, has two mutations in the causative gene, *TYRP1*. The wild-type allele, *B*, which causes normal black pigment, is dominant to the brown allele,

b, which causes a reduced amount of black pigment, producing a more brownish hue to the fur. The brown allele, *b*, is considered dominant to light brown, whereas *b^l* imparts a cinnamon-color or reddish effect on the fur. The allelic series is written as: *B* > *b* > *b^l* to indicate the dominance of one allele over the other. In the case of the *Color* locus, *C*, which is also an allelic series, the sepia coloration, *c^bc^b*, which is fixed in the Burmese (Figure 44-1) and Singapura (Figure 44-2) breeds, is co-dominantly expressed with the Siamese points, *c^sc^s*, producing an additive effect. Thus compound heterozygous cats, *c^bc^s*, have an intermediate coloration compared with that of the Burmese and the Siamese; this is usually referred to as a *mink Tonkinese* (Figure 44-3). Complete albinos, which have an additional allele at the *Color* locus, have been identified. The locus is controlled by the gene

TABLE 44-2 Other Mutations for Inherited Domestic Cat Diseases*

Disease	Gene	Mutation	Disease	Gene	Mutation
Gangliosidosis 2 ⁶⁹	<i>HEXB</i>	inv1467-1491	Mucopolysaccharidosis VI ^{22,101}	<i>ARSB</i>	G1558A
Gangliosidosis 2 ⁵¹	<i>HEXB</i>	C667T	Mucopolysaccharidosis VII ²⁹	<i>GUSB</i>	A1052G
Gangliosidosis 2 ⁶⁸	<i>GM2A</i>	del390-393	Muscular dystrophy ¹⁰⁰	<i>DMD</i>	900bp del M promoter -exon 1
Hemophilia B ⁴⁰	<i>F9</i>	G247A	Niemann–Pick C ⁹¹	<i>NPC</i>	G2864C
Hemophilia B ⁴⁰	<i>F9</i>	C1014T	Polydactyla ⁵⁸	<i>SHH</i>	A479G
Hyperoxaluria ³⁹	<i>GRHPR</i>	G>A I4 acceptor site	Polydactyla ⁵⁸	<i>SHH</i>	G257C, A481T
Lipoprotein lipase deficiency ³⁸	<i>LPL</i>	G1234A	Porphyria ¹⁹⁻²¹	<i>HMBS</i>	c.842_844delGAG
Mannosidosis, alpha ⁹	<i>LAMAN</i>	del1748-1751	Porphyria ¹⁹⁻²¹	<i>HMBS</i>	c.189dupT
Mucolipidosis II ⁷⁰	<i>GNPTA</i>	C2655T	Vitamin D-resistant rickets ³⁷	<i>CYP27B1</i>	G223A, G731del
Mucopolysaccharidosis I ⁴⁵	<i>IDUA</i>	del1047-1049	Vitamin D-resistant rickets ⁴²	<i>CYP27B1</i>	G637T
Mucopolysaccharidosis VI ¹⁰²	<i>ARSB</i>	T1427C			

*The presented conditions are not prevalent in breeds or populations but may have been introduced into research colonies.

TABLE 44-3 Simple Phenotypic Traits and Diseases of the Cat and Its Breeds: Mutations Are Unidentified

Locus	Phenotype	MOI	Locus	Phenotype	MOI
Bobtail	Curly and kinked tail	AD, variable expression	<i>Orange</i>	Orange hue to pigment	X-linked
Craniofacial Defect	Skull structural closure abnormality common to Burmese	AR	Peterbald	Brush coat, hairless	ID
Ear curl	Pinnae curl rostrally	AD	Rexing	Curly coat	AD
Ear fold	Pinnae folds ventrally	AD	Rexing	Curly coat	AR
Hypokalemia	Potassium insufficiency	AR	<i>Spotting</i>	Bicolor white	AD
<i>Inhibitor</i>	No pheomelanin	AD	<i>Tabby</i>	Type of tabby pattern	AS
Lymphoma	Mediastinal in Oriental breeds	AR	<i>Ticked</i>	Production of a tabby pattern	AD
Manx	Tailless, short tail	AD, variable expression	<i>White</i>	Dominant white, no pigment	AD
Myopathy	Generalized muscle weakness	AR	Wirehair	Wired coat	ID

MOI, Mode of inheritance (of the mutations as compared to the wild-type allele); AD, autosomal dominant; AR, autosomal recessive; ID, incomplete dominance; AS, allelic series. Orange is the only X-linked phenotypic trait.



FIGURE 44-1 Burmese. (Photo copyright 2011 Richard Katris.)



FIGURE 44-2 Singapura. (Photo copyright 2011 Richard Katris.)



FIGURE 44-3 Tonkinese. (Photo copyright 2011 Richard Katris.)



FIGURE 44-5 Devon Rex. (Photo copyright 2011 Richard Katris.)



FIGURE 44-4 Cornish Rex. (Photo copyright 2011 Richard Katris.)



FIGURE 44-6 American Wirehair. (Photo copyright 2011 Richard Katris.)

tyrosinase; TYR and the allelic series is written as $C > c^b = c^s > c$.

The coat color mutations are common to all cats and are effective for genetic typing in all breeds and populations. However, even though long fur is common in pedigree and random-bred cats, long fur is an exception because four different mutations in the gene *fibroblast growth factor 5* (*FGF5*) can cause a cat to have long fur.^{25,52} One mutation is common to almost all breeds and populations, which suggests that this mutation is the most ancient and present before breeds developed, but the other long fur mutations are more specific to particular breeds.³ Some cats can have long fur because of two different mutations in the gene *FGF5*. These cats would

be considered compound heterozygotes. Thus all four mutations must be genotyped to determine whether a cat carries a mutation for long fur.

Rexing is an interesting set of mutations for the domestic cat. At least six different types of rexoid mutations have been noted in the cat, including Cornish Rex (Figure 44-4) and Devon Rex (Figure 44-5), as well as several unpublished varieties, including American Wirehair (Figure 44-6), Selkirk Rex (Figure 44-7), LaPerm (Figure 44-8), and Tennessee Rex. The Devon Rex and



FIGURE 44-7 Selkirk Rex. (Photo copyright 2011 Richard Katris.)



FIGURE 44-8 LaPerm. (Photo copyright 2011 Richard Katris.)



FIGURE 44-9 Sphynx. (Photo copyright 2011 Richard Katris.)

Cornish Rex had been known to be caused by different genes after cross-breeding experiments and genetic studies.³⁵ The genetic studies have ruled out the Devon Rex gene, *keratin 71* (*KRT71*), as causative for the other rexoid cats.³⁵ The Selkirk and LaPerm have dominant mutations, Devon and Cornish are caused by recessive mutations, and the wirehair appears to be a dominant mutation with variable expression and even incomplete penetrance, wherein sometimes cats thought to have the mutation are not wirehaired. Sometimes two traits are not initially known to be caused by the same gene, such as hairlessness of the Sphynx and rexing in the Devon Rex.^{35,86} Thus the hairlessness of the Sphynx (Figure 44-9)

has had the locus name *Hairless* with alleles *Hr* and *hr*, whereas Devon Rex has had the locus name of *Rex* with alleles *Re* and *re* defining Devon Rex as a separate locus from *Rex*, with alleles *R* and *r* for the Cornish Rex. Both Sphynx and Devon Rex have been proved to be caused by mutations in *KRT71*.³⁵

Orange is the only trait known to be on the X chromosome for the domestic cat.^{5,24,46,62} Because the X chromosome is subject to X inactivation in females, female cats that are heterozygous for the *Orange* and wild-type black alleles will express the coloration associated with the allele that is on the active X chromosome. Because X inactivation is random and occurs early in



FIGURE 44-10 Manx. (Photo copyright 2011 Richard Katris.)



FIGURE 44-11 Scottish Fold. (Photo copyright 2011 Richard Katris.)

embryogenesis, the melanocytes in the skin will have different inactive X chromosomes, leading to the brindled black and orange of a tortoiseshell cat. Combined with the *Spotting* locus, which affects melanocyte migration and distribution, larger patches of skin will be covered by a clonal melanocyte population that has the same X inactivation, leading to large patches of orange or black or white coloration. Thus only female cats should be tortoiseshell or calico. Calico and tortoiseshell male cats are discovered fairly frequently, but they are usually sterile because they are genetic chimeras, having some cells as XX and some as XY. Chimeras are likely to be caused by the fusion of two embryos very early after fertilization.*

Mutations that affect structural traits, such as Manx (Figure 44-10) and ear fold (Figure 44-11) or curl (Figure 44-12), have a tendency to be dominant mutations. Two copies of a dominant mutation are often highly detrimental. Kittens that are homozygous for the Manx mutation die in utero,⁸⁷ and many cats homozygous for ear fold suffer from osteochondrodysplasia.^{17,67,80,92} However, cats homozygous for ear curl have no known detrimental health effects, nor do homozygous Japanese Bobtails (Figure 44-13). Most of the dominant mutations have only one known allele, except for polydactylism, in which several causative alleles have been noted in the gene *sonic hedgehog* (*SHH*).⁵⁸ Compound heterozygote cats for polydactylism mutations have not been identified, so the effects of having two different mutations that cause polydactylism are not known. Homozygote cats for a polydactyl mutation have been identified and do not necessarily have a more severe presentation, such as several extra toes or additional abnormalities to the digits (Lyons LA, unpublished data).



FIGURE 44-12 American Curl. (Photo copyright 2011 Richard Katris.)

Two genetic mutations of the domestic cat are not associated with a disease or a phenotypic trait. Cats have been shown to have mutations in a gene, *TAS1R2*, that disrupts the sweet receptors.^{60,61} This mutation can be used to determine if an unknown DNA sample is of feline origin. Another example is the mutation that causes B blood type in cats.¹¹ Blood type incompatibilities obviously can lead to transfusion reactions and neonatal isoerythrolysis for the cat, but inherently this characteristic is not necessarily a disease. A point mutation and an 18 base pair deletion have both been implicated in the gene *CMAH* as indicating the presence of the B blood type, or a B blood type carrier. Because both mutations are on the same allele, a clear indication of the

*References 16, 18, 43, 49, 55, 56, 83, 94.



FIGURE 44-13 Japanese Bobtail. (Photo copyright 2011 Richard Katris.)

true causative mutation could not be determined. Thus both mutations should be examined in cats to genetically determine blood type.

Disease Mutations of the Domestic Cat

Many cat mutations that cause heritable diseases have been identified by way of the candidate-gene approach. Often, different biomarkers can identify possible inborn errors of metabolism, which lead to lysosomal storage diseases, such as gangliosidosis and mucopolysaccharidosis. Interestingly, both gangliosidosis 1, caused by *GLB1* mutations, and gangliosidosis 2, caused by *HEXB* mutations, both found in the Korat breed, were some of the early discoveries of genetic mutations in the cat.^{23,76} The clinical presentations strongly suggested conditions that were similar to those found in humans and other species. Because causative mutations had already been identified in these other species, the genes became obvious candidates for the cat. These mutations were identified at a time when significant genome sequence was not available for the cat; therefore, although a strong candidate was indicated, the studies were tedious. *Dystrophin*, the gene that causes Duchenne and many other types of muscular dystrophy, is a significantly large gene, and early studies discovered a feline mutation causing a similar dystrophy in the cat.^{1,100} Cats having several of the diseases that were discovered early are actively retained in colonies because they are important models for gene therapies and many young children suffer from the same diseases as found in the cat.

Many of the disease mutations in the cat were identified in random-bred cats, such as hemophilia B⁴⁰ and vitamin D-resistant rickets,³⁷ or in a specific individual of a breed and are not a concern to the breed population in general, such as Niemann–Pick type C⁹¹ and mannosidosis in Persians.⁹ These breed-identified genetic mutations should not be part of routine screening by cat

breeders and registries, but clinicians should know that genetic tests are available for diagnostic purposes, especially from research groups with specialized expertise, such as at the University of Pennsylvania (<http://research.vet.upenn.edu/penngen>). Unlike coat color mutations, which are common in the random-bred cat, the disease mutations are infrequent and should not be considered for genetic typing unless a clinical presentation is indicative of the disease. Even then, the clinical presentation may be more accurate for defining the disease as a new mutation in a known gene could be as likely in a random-bred population as the rediscovery of an already identified mutation. Several independent mutations have been identified in *HEXB* for gangliosidosis,^{14,51,69,76} in *ARSB* for mucopolysaccharidosis VI,^{22,101,102} and *HMBS* for porphyria.¹⁹⁻²¹ A genetic test could rule out these mutations, although other mutations could also be present.

Like the Korat with gangliosidosis, the Abyssinian breed has had two different disease forms identified for a specific type of disease: progressive retinal atrophy (PRA). Mutations for both an early-onset, rapidly progressing autosomal dominant PRA, *CRX*,⁷³ and a late-onset, slowly progressing autosomal recessive PRA, *CEP290*, have been identified in Abyssinians.⁷² Abyssinians also have a recessive trait causing deficiency of the enzyme pyruvate kinase in red blood cells, as well as cats in the breed population with different blood types. Therefore Abyssinian breeders commonly use genetic testing in breeding programs. The Abyssinian is one of the oldest cat breeds, present during the early foundations of cat registries. This breed's genetic heritage is obscure; it is not clearly a cat of eastern or western origins, although some evidence suggests that it may have originated in India. Historically, the breed has been fairly popular around the world, and genetic population statistics do not indicate that the Abyssinian breed is of any more or less concern for inbreeding depression than any other cat breed. Thus the detection of these various diseases in the Abyssinian may be an ascertainment bias or just sporadic bad luck for the breed.

Other diseases, such as PKD, are prevalent; PKD in Persians is estimated at 30% to 38% worldwide.^{78,15} Because of cross-breeding with Persians, many other breeds, such as British Shorthair, American Shorthair, and Scottish Fold, also should be screened for PKD.^{12,26,64} Thus veterinarians need to be aware of cross-breeding practices, which vary among different cat registry organizations, so that genetic tests can be placed as high or low priorities for differentials and diagnostics.

Unidentified Genetic Diseases and Traits of the Domestic Cat

Hundreds of traits and diseases that have been recognized to be genetic in other species have been

documented in the domestic cat and its breeds (see Online Mendelian Inheritance in Animals: <http://www.ncbi.nlm.nih.gov/omia>). However, an increased incidence and prevalence must be documented before accepting that a single case report or case series of a condition constitutes a genetic problem for a breed or a population. Those traits with as yet unidentified mutations and a strongly suggestive mode of inheritance are presented in Table 44-3.

Breed dispositions to diseases, which may be due to genetics, environment, or both, have been reviewed for dogs and cats.⁴¹ Common environmental factors are often difficult to identify and consider. Veterinarians should note that populations change genetically over time, and breeders have an impact on undesired traits through selection; thus conditions documented in the past may not be of present concern or risk. As previously mentioned, because breed populations vary greatly in different parts of the world, breed risks for diseases and health conditions vary accordingly. Many cat breeders and registries are proactive and openly list and discuss health concerns for their breeds. Overall, effective genetic studies to find mutations that cause health issues and traits require a sufficient sample size, which generally means active participation from the breed group.

Many of the morphologic and structural presentations of the domestic cat breeds may influence the presentation of conditions that are then noted to have a higher prevalence in a breed. Already mentioned are incontinence in the Manx and osteochondrodysplasia of the Scottish Fold. These health conditions are actually secondary effects of the primary genetic mutation. The brachycephalia of Persian cats and related breeds has caused significant concern on account of the secondary structural abnormalities and chronic health problems caused by the extreme shortening of the skull.^{57,89,90} Anecdotally, the fine, elegant structures of Abyssinians and Siamese exacerbate patellar luxation. The largest breed, the Maine Coon, may be affected by hip dysplasia, a very common problem in large dog breeds.

GENETIC RISK FACTORS AND COMPLEX TRAITS

All the mutations influencing a disease may not be identified at any given time; usually the mutations that influence a condition the most and have the highest heritability are identified first. Because multiple mutations may act additively to cause a disease, each mutation may be said to confer a "risk" for disease development. Thus some mutations may be considered risk factors, predisposing an individual to a health problem. These risk-conferring mutations are neither necessary nor sufficient for causing disease. An excellent example of a mutation that confers

a risk are the DNA variants associated with cardiac disease in cats.

Hypertrophic cardiomyopathy (HCM) is a recognized genetic condition in cats.⁵³ In 2005, Meurs, Kittleson, and colleagues reported that a DNA alteration in the gene *cardiac myosin-binding protein C 3 (MYBPC3)* was strongly associated with HCM in a long-term research colony of Maine Coon cats at the University of California, Davis.⁷⁵ The DNA mutation is commonly referred to as *A31P* because this DNA mutation changes codon 31 from an alanine to a proline in the amino acid sequence (i.e., protein) of *MYBPC3*. The data clearly show that not all cats with the mutation had HCM and that some cats with HCM did not have the DNA mutation. Age of onset, variable expression, and disease heterogeneity were mentioned in this report. These aspects suggest that the identified DNA variant should be considered more of a risk factor than a directly causative mutation. Two recent papers have shown that not all Maine Coon cats with the *A31P* mutation develop HCM,^{88,98} and one of those papers has mistakenly interpreted this lack of penetrance as being evidence that the *A31P* mutation is not causal.⁹⁸ This interpretation is misleading, causing debate about the validity of the Maine Coon HCM test.

To date, most cat genetic tests have been for traits that have nearly complete penetrance, have little variability in expression, and are early in onset. However, some imperfect examples do exist in cats that have not caused as much controversy as the HCM test. The *CEP290 PRA* mutation in Abyssinians has a late age of onset, and some cats with subclinical disease have been identified.⁷¹ Some cats with pyruvate kinase deficiency have very mild and subclinical presentations.⁵⁴ The interplay of various coat color genes often muddles the determination of the true coat color of cats. As is true in humans with cardiac disease, the finding that not all cats with the *A31P* mutation in *MYBPC3* develop HCM is actually more commonplace in the field of HCM genetic testing. Because disease- or trait-causing mutations may not be 100% penetrant, they do not always cause clinically detectable disease. Presence of clinical disease in an individual cat and the severity of disease (expression) are likely affected by the known genetic aspects presented in the subsequent sections.

Incomplete Penetrance

For some traits and diseases, even though a known causative mutation has been identified, an individual with that mutation does not present with the condition. Incomplete penetrance is an extreme of variable expression (discussed in more detail later in this chapter). In general, the reason that a condition associated with a mutation would not be present is unknown, but other genetic, biologic, and environmental interactions

certainly play a role in the overall appearance and health of an individual and its organs. The sensitivity of clinical diagnostics may also influence the determination of penetrance. In the case of HCM, echocardiography can be considered an insensitive tool for detecting mild forms of the disease in cats; thus many cats with mild changes do not clinically appear to have cardiac disease. Experience and bias also play a role in diagnosis. For example, individuals who do not have expertise in the use of ultrasonic examinations for HCM or PKD are less likely to be able to provide an accurate diagnosis for these diseases.

Age of Onset (Age-Related Penetrance)

Some diseases have a slow progression and may not present until later in life. In humans HCM caused by *MYBPC* mutations is clearly a disease that has slow progression and commonly does not express until the individual is over 50 years of age. HCM in Maine Coon cats can also develop in older cats, especially in cats that are heterozygous for the mutation and, for some unknown reason, in females. Often, an autosomal dominant disease may be more severe if two copies of the risk mutation are present in an individual, leading to earlier and more severe disease, which appears to be the case with the A31P mutation. The definitive age as to when a cat is past the risk of developing HCM is not precisely determined.

Variable Expression

Most traits and diseases have some amount of variable expression depending on the individual. For example, not all cats with the mutation for blue dilution have the same color of blue-gray fur. Obviously, the background genetics and environment of the individual influence the overall presentations of traits and diseases. Thus the level of presentation can be variable in regard to left ventricular wall thickness in cats with HCM. Cats can have mild, moderate, or severe HCM. Only those cats with severe HCM show clinical signs, although a few cats with lesser severity of disease may die suddenly. Cats with HCM may fall in the "equivocal" range for wall thickness; therefore definitive disease status is difficult to declare. These equivocal cats may progress to more severe disease with time, or the equivocal status may be as severe as the disease gets. Some cats with PKD have only a few cysts and never progress to renal failure while others have severe and fast progression of disease and succumb to renal failure in a few years.

Disease Heterogeneity

More than one mutation in the same gene or mutations in different related genes can cause the same disease.

Genetic heterogeneity for HCM in humans is well established, and there is no reason to think the same situation is not true for cats. Currently, more than 1000 mutations in more than 10 genes are known to cause HCM in humans. Only two mutations have been identified that cause HCM in cats, the A31P mutation in Maine Coon cats and the R820W mutation in Ragdolls,^{74,75} which also causes disease in humans.⁸⁴ Both mutations are in *MYBPC3*, the most commonly mutated gene in humans with HCM (see review by Tsoutsman et al⁹⁶). Other breeds of cats, including the Bengal, Siberian, Devon Rex, and Sphynx, and random-bred cats either do not have or have an extremely low prevalence of the A31P or the R820W mutation. However, because there are Maine Coon cats that have HCM and do not have the A31P mutation, there must be at least one more cause of HCM, most likely another mutation, in this breed. The long fur mutations in the cat are also examples of trait heterogeneity.

Accuracy of Genetic Testing

Even though a specific genetic mutation may be identified for a trait or disease, research laboratories use different methods to assay for the mutation. Errors in genetic assays may produce inaccurate DNA results, leading to confusion in genetic test interpretation. Direct DNA sequencing is considered the most robust method, "the gold standard," but it is also one of the more costly methods of analysis. Because DNA primers must bind to the DNA sequence flanking a specific mutation, other, unimportant mutations may be in the areas where the primers bind, causing poor or no amplification of one or both alleles for a given individual. This condition is known as allelic dropout, and all testing laboratories are aware of this potential source of error for a genetic test. Even direct DNA sequencing can suffer from allelic dropout, but because a larger portion of the gene that may have other DNA variants is generally amplified, a higher likelihood of detecting allelic dropout is present. Laboratories will place polymerase chain reaction (PCR) primers in different locations surrounding the mutation of interest, which is often proprietary information, in attempts to lower the risk of allelic dropout. Thus some laboratories have better assays than others, even if they are doing the same assay method and testing for the same mutation. The different DNA assay methods are usually developed to reduce cost and fit the laboratory's expertise and instrumentation. However, some assays may have, in general, an increased risk of test failure. Common methods for DNA testing include real-time PCR (TaqMan), restriction fragment length polymorphism (RFLP), allele-specific oligonucleotides (ASOs), or even mass spectroscopy-based methods. Just as a veterinarian may want to know if a feline immunodeficiency virus (FIV) test is performed by enzyme-linked

immunosorbent assay (ELISA), PCR, or Western blot because each method has different sensitivities and specificities, this is also true for DNA-testing methods. Veterinarians will need to become familiar with the different genetic testing approaches and not hesitate to ask testing laboratory staff members about their methods and sensitivity and specificity for their approaches.

Inaccurate Clinical Diagnosis

Echocardiography is the most common and currently the only useful method for diagnosing cardiac disease in cats. Several studies have evaluated HCM in domestic shorthair and Maine Coon cats.^{28,44,79} Not all cardiac disease is HCM, and even the definition of HCM can be debated. A consistent definition for HCM is not used by all cardiologists, which creates difficulty when correlating a genetic test result with an ultrasound report, especially if detailed diagnostic criteria are not presented in the report. Misinterpretations in ultrasound examinations may lead to different interpretations with disease status.

Overall, the only way to determine the true risk conferred by some mutations is to follow cats over the course of a lifetime with common diagnostic procedures and compare outcomes to the genetic test results. Only time and continued follow-up will help determine the true relative risk that mutations convey for complex diseases. In the case of HCM, various studies have indicated higher or lower risks in different populations of cats, but none has been able to follow cats throughout a lifetime. These studies are important and are of great value to the community. Other mutations must be found, and the cooperation of breeders must be positive and enthusiastic for these studies to succeed.

GENETIC TESTING

Breeding Recommendations

Cat breeders are very knowledgeable about weighing different factors to produce healthy cats that are of good physical type and temperament. Many genetic tests help a breeder make a clearer, more educated decision. Cats with a positive genetic test for a disease should be screened by another diagnostic method, such as ultrasound in the case of HCM and PKD, to determine disease status, and this overall information should be used in breeding decisions. Other health, physical type, and behavioral attributes should certainly be considered in the overall breeding program. However, breeders should work hard to reduce the risks with any health issue. Every cat that has the HCM A31P mutation is at risk for developing HCM, and every cat with the mutation will pass it on to some or all offspring. Cats that are

homozygous for the A31P mutation will definitely pass the mutation to all offspring. The homozygous cats are at higher risk of developing severe HCM. Cats that are heterozygous for the mutation should not be bred unless they have other qualities that are either highly beneficial or necessary to the breed. Kittens that test negative for the mutation should be used to replace affected parents in the gene pool. A slow eradication of disease is recommended for highly prevalent diseases, such as HCM and PKD, because the quick elimination of a high number of cats could lead to other effects of inbreeding depression. Breeders of cat breeds with very low population sizes, such as the Korat, have learned to manage the gangliosidoses by never breeding carriers together. It is to be hoped that all the disease mutations can eventually be eradicated, but good breeding decisions and balancing population diversity must be considered.

Recently, estimated breeding values (EBVs) have been suggested as a means to apply selection to companion animal populations.^{59,93} EBVs are not a new concept; they are used to assign a value to an animal based on selected qualities. Cat and dog breeders inherently assign EBVs to their breeding stock, but not in a preset and defined numeric fashion. The dairy and beef industries have used EBVs for decades to produce herds that have higher milk yields, milk fat content, or different carcass qualities. Generally, some industry standard has to be developed and routinely followed in the same direction of positive or negative selection for the trait(s) of interest. EBVs usually pertain to traits that are complex and have some quantitative measurement, such as weight, height, or tail length. Thus standard quantitative genetic techniques can be used to estimate the extent of inheritance of the disorder (heritability), followed by the development of a metric that can be used to assess the genetic merit of individual animals for the purpose of selection for reproduction and subsequent breed improvement. In the simplest form, cats that carry undesired traits, such as a disease, should be assigned a low EBV. However, other desired traits may outweigh the negative value of a disease or condition, giving a cat an overall high EBV. EBVs are a concept to consider as more genetic tests are developed because breeders now have more informative data to consider when selecting mating pairs for the propagation of a breed. Standards and a unified effort would need to be developed, as well as retrospective trials to model the effects of the EBVs before they are implemented.

Genetic Testing Concerns in Different Breeds or Populations

Once a mutation is identified for a gene that causes a particular coat color or disease, a service laboratory, either in association with the investigator who found the

mutation or an independent commercial laboratory, will establish a genetic test for that mutation to offer to the public (Table 44-4). Over a dozen laboratories around the world now offer genetic testing for PKD in cats. All the laboratories may be technically accurate, but not all of them “know their cats” equally. Some of the concerns with specificity and sensitivity of genetic tests, particularly in regard to testing in hybrid cat breeds, are due to

a lack of knowledge of how cat breeds are developed and cat evolutionary relationships.

Tables 44-1 and 44-2 contain all the currently known genetic mutations in the cat that have been published and may be of concern for genetic testing. Genetic diseases usually present in a specific breed and thus are associated only with that breed. However, some breeds are allowed to outcross with others, and some are legally

TABLE 44-4 Domestic Cat DNA Testing Laboratories

Lab/Website	Region	University Research Affiliate	ID	Cat Test*			Blood	Coat
				Disease	Color			
Animal DNA Testing www.animalsdna.com	Australia		Yes	4	Some		Yes	No
Animal Health Trust www.aht.org.uk	UK	Animal Health Trust	Yes	PKD	No		No	No
Antagene Immeuble Le Meltem www.antagene.com	France		Yes	4	Color		Yes	No
BioAxis DNA Research Centre Ltd. www.dnares.in	India		Yes	PKD	No		No	No
DNA Diagnostics Center www.dnacenter.com	U.S.		No	PKD	No		No	No
GENINDEXE www.genindexe.com	France		Yes	7	5		Yes	No
Genoscoper www.genoscoper.com	Finland		Yes	No	No		Yes	No
Gribbles www.gribblesvets.com	Australia		No	PKD	No		No	No
IDEXX www.idexx.ca	Canada		No	PK def.	No		No	No
Laboklin www.laboklin.de/	Germany		Yes	9	5		Yes	Long
Langford Veterinary Services, Molecular Diagnostics Unit, Langfordvets.co.uk	UK	Bristol	No	3	No		No	No
PennGen research.vet.upenn.edu/penngent	U.S.	Pennsylvania	No	PK GSD	No		No	No
PROGENUS S.A. www.progenus.be	Belgium		Yes	HCM PKD	No		No	No
Van Haeringen Laboratory www.vhlgenetics.com	Netherlands		Yes	9	5		Yes	Long
Veterinary Cardiac Genetics Lab www.cvm.ncsu.edu/vhc/csds/vcgl	U.S.	North Carolina State	No	HCM	No		No	No
Veterinary Genetics Lab www.vgl.ucdavis.edu	U.S.	California, Davis	Yes	7	All		Yes	All
VetGen www.vetgen.com	U.S.	Michigan	Yes	No	Brown dilute		No	Long
Vetogene www.vetogene.com	Italy	Milan	Yes	HCM PKD	No		No	No

PKD, Polycystic kidney disease; GSD, glycogen storage disease; HCM, hypertrophic cardiomyopathy; ID, individual genetic identification; PK def., pyruvate kinase deficiency.

*Tests reference to those listed in Table 44-1. If a laboratory offers only one or two tests, those tests are listed. PKD and HCM are the most popular tests to offer.

†PennGen also offers tests for diseases in Table 44-2 that are not of concern to the cat breeds or population in general.

or illegally used to help refine the appearance of another breed. The Siamese and Persian have influenced a host of other cat breeds. Hence any mutation found in one breed can be found in others if cross-breeding has occurred. In addition, cats are bred all over the world, and the rules of various registries and associations are not always the same. An outcross that may be acceptable for The International Cat Association⁹⁵ in the United States may be unacceptable for the Cat Fanciers' Association or perhaps the Governing Council of the Cat Fancy³⁶ in the United Kingdom. Thus the personnel of testing laboratories must understand cat breed dynamics to know whether a test is valid for a given breed in any part of the world and to offer the appropriate tests for the breeds at risk.

Why does one care if a genetic test developed in one breed is valid in a different breed? The concern is disease heterogeneity. Owners, breeders, and veterinarians may identify a clinical presentation that is abnormal in the cat, but they also may jump to conclusions too quickly. For example, there are many causes of renal failure besides PKD. There are different types of cardiac disease; not all cardiac disease is HCM. Even when a diagnosis of HCM is definitive, not all HCM is caused by the same mutation. Herein lies the concern. An unknowing veterinarian, owner, or breeder may want a cat to have a genetic test for HCM or PKD because the cat has clinical signs consistent with these diseases. If the test shows a negative result, this result does not necessarily mean the cat does not have HCM or PKD, if the test has not been proved effective in that selected breed. The result does imply that the cat does not have the mutation causing Maine Coon or Ragdoll HCM or Persian PKD. A laboratory may very well run the test, but laboratories have different capabilities and skills with genetic counseling. Veterinarians may be on their own when it comes to interpreting the meaning of a negative test. This is why a test is generally listed as pertaining to a specific breed. Until clinical data (e.g., ultrasound diagnoses and genetic test results) is available from a sufficient number of cats, a test cannot be valid for the breed unless clear outcrossing to the risk breeds is apparent.

Genetic Testing Concerns in Hybrid Cat Breeds

Some domestic cat breeds are hybrids of two species of cats. According to the biological species concept, organisms are classified in the same species if they are potentially capable of interbreeding and producing fertile offspring. The production of hybrid cat breeds generally has required a female domestic cat to be bred with a male cat from another wild felid species because of temperament concerns. For example, domestic cats have been bred to Asian Leopard cats to produce the

Bengal and to the Serval to produce the Savannah. For the first-generation offspring, or first filial (F1) generation, of hybrid cat breeds, the male F1 is sterile; the subsequent generations cannot be produced by crossing a male F1 with a female F1. Thus the female F1 offspring are generally mated with a full-blooded domestic male or a lower-generation hybrid male that is fertile. Cat breeders will term the subsequent generations of offspring as F2, F3, and so on; however, these designations are actually genetically incorrect, and they should be considered backcross generations (e.g., BC1, BC2). The F1 females are also difficult to mate and may have reduced fecundity. Fertility may take several generations to re-establish in hybrid breeds. The infertility is due to problems with chromosomes aligning during cell reproduction for the production of the gametes, as well as allelic incompatibilities at different genes. Because the inheritance of the allelic incompatibilities is difficult to predict, many hybrid cats can have reproduction problems, even in the lower generations that can be shown in competition.

A normal level of genetic variation among cats is expected, typically far less than 1% of a sequence that codes for a protein. Herein lies a problem for hybrid cat breeds. The evolutionary time between the appearances of different cat species is millions of years,⁵⁰ not the hundreds to thousands of years between the appearance of cat breeds and populations. An Asian Leopard cat had a common ancestor with the domestic cat about 6 million years ago, the Bobcat about 8 million years ago, and the Serval about 9.5 million years ago. The Jungle cat is more closely related to the domestic cat than the Asian Leopard cat is. In addition, for some of these wild felid species, different subspecies have been incorporated into the breed. The DNA sequence of a domestic cat and one of these wild felid species will have many genetic differences, maybe a several percentage difference, less for the jungle cat, more for the Serval compared with that of a domestic cat. The genetic differences are most likely silent mutations, but the variation will interplay with genetic assays and may cause more allelic dropout than what would be normally anticipated. No genetic tests have been validated in the hybrid cat breeds, although they are used frequently. As mentioned, these allelic differences can cause allelic incompatibilities, which could produce reproduction problems and other health issues.

Most laboratories recognize that disease mutations are specific to breeds but not the coat colors. The coat color mutations occurred during the early domestication of the cat, before the breeds were developed, so all breeds tend to have the same mutation. This is true for all the coat color tests so far but for the hybrid breeds, such as the Bengal, Chausie (produced from the jungle cat), and Savannah, some oddities in coat color and disease testing may occur. The normal DNA sequence

around each of the mutations for coat colors must be evaluated in many individuals from each wild felid species to find the normal, silent mutations that occur between the wild felids and the domestic cats. At any given gene, in a Bengal, it cannot be determined whether one Asian Leopard cat sequence or two are present. Thus the accuracy for any genetic test is not known for hybrid cat breeds. If the domestic cat alleles are present, the test will perform as expected. However, one never knows when one allele or both are from the Asian Leopard cat. Selection generally favors the wild felid colorations, so inherently the breed is selected for the DNA sequences that may cause the genetic tests to fail.

Inappropriate Genetic Testing Laboratory Procedures

Genetic testing laboratories attempt to provide the best service for the lowest cost. Many of the newer technologies allow for higher throughput of samples and also performance of more than one genetic test per assay, greatly lowering costs of reagents and human labor. Many testing laboratories aspire to be as complete as possible, providing all available genetic tests for any given species. However, in the zeal of competition, a few genetic tests that are offered in the cat do not have sufficient scientific support. Any genetic test should be based on a reference publication to determine the genetic sequence surrounding the mutation and provide the statistical support for the accuracy of the mutation for conferring disease or the trait of interest in specific breeds and populations. Published abstracts are not peer-reviewed articles and do not provide sufficient information to determine the accuracy of a test; thus abstracts are not appropriate references for genetic tests. Some universities or researchers own associated companies, the discoveries of which may be protected by licensure or patent, and the data may never be published for competitive advantage. Some genetic tests therefore can be found only with specific testing companies. Currently, the patented tests for cats include PKD, HCM, the mutations for *Tyrosinase* at the *Color* locus that confer Siamese and Burmese style "points," and blood type B.¹¹ However, licensure is available for each of these tests and the patents pertain only to the United States. Some companies will violate these patents because the overall income to the patent holder is generally very low and the likelihood that a university would enforce a patent would be low relative to the prohibitive cost. However, violation of genetic test patents is not encouraged and is generally considered inappropriate.

In addition to violating patents, some laboratories offer genetic tests that are not scientifically sound in an attempt to gain a competitive advantage. Another mutation in *MYBPC3* for HCM was reported in an abstract

but was never presented in a peer-reviewed publication. Support for the risk this mutation confers for HCM in cats has not been well documented, but some laboratories nonetheless offer testing for this DNA variant. Laboratories often post disclaimers, leaving the veterinarian, owner, and breeder to speculate about a test's true diagnostic utility.

Some laboratories offer a single method, such as a type DNA array method, to genetically test all mutations for the cat. As noted in **Tables 44-1 and 44-2**, the mutations that cause traits and diseases of the cat come in a variety of types. Many mutations are point mutations: a single nucleotide difference in the DNA. Others are deletions of one or more bases, and some are very complex alterations that can disrupt several exons of a gene, such as the mutation that causes spinal muscular atrophy in the Maine Coon cat. The genetic sequence surrounding a mutation is also important because some regions may be rich in particular bases, such as a GC-rich region or a region with repeat elements of stretches of similar nucleotides, such as polyadenosine stretches. This information is less important to the veterinarian, but very important to the development of an assay that is sound and efficient. A single testing method, such as size variation, RFLP, real-time PCR (TaqMan), or any array method cannot effectively test all the different mutations. Thus a testing laboratory must be proficient in several methods to test all types of mutations for the cat or any other species. Veterinarians should be skeptical of any laboratory that offers one testing method for all mutations of the cat.

CONCLUSION

Genetic testing is an important diagnostic tool for the veterinarian, breeder, and owner. Genetic tests are not 100% foolproof, and the accuracy of the test procedure and the reputation and customer service of the genetic testing laboratory must be considered. Some traits are highly desired, and genetic testing can help breeders determine appropriate pairings more accurately. This may encourage more efficient breeding programs, thereby lowering costs and excessive cat production. Other traits or diseases are undesirable, and genetic testing can be used to prevent and potentially eradicate them from the population. Genetic tests for simple genetic traits are more consistent with predicting the trait or disease presentation, but as genomics progresses for the cat, tests that confer risk will become more common. Veterinarians will have to weigh the relative risks of having a mutation versus having disease as part of the differential diagnosis, and breeders will have to consider risk factors along with the other important attributes of a cat in making breeding decisions.

References

1. Allamand V, Campbell KP: Animal models for muscular dystrophy: valuable tools for the development of therapies, *Hum Mol Genet* 9:2459, 2000.
2. American Pet Product Manufacturing Association: *National pet owner's survey*, Greenwich, Conn, 2008, The Association.
3. Bach L, Gandolfi B, Grahn R et al: The distribution and possible origins of FGF5 mutations affecting fur length in cats, *submitted for publication*, 2011.
4. Bamber RC: Correlation between white coat colour, blue eyes, and deafness in cats, *Journal of Genetics* 27:407, 1933.
5. Bamber RC, Herdman EC: The inheritance of black, yellow and tortoiseshell coat colour in cats, *J Genet* 18:87, 1927.
6. Banks G, Chamberlain J: The value of mammalian models for duchenne muscular dystrophy in developing therapeutic strategies, *Curr Top Dev Biol* 84:431, 2008.
7. Barrs VR, Gunew M, Foster SF et al: Prevalence of autosomal dominant polycystic kidney disease in Persian cats and related-breeds in Sydney and Brisbane, *Aust Vet J* 79:257, 2001.
8. Barthez PY, Rivier P, Begon D: Prevalence of polycystic kidney disease in Persian and Persian related cats in France, *J Feline Med Surg* 5:345, 2003.
9. Berg T, Tollersrud OK, Walkley SU et al: Purification of feline lysosomal alpha-mannosidase, determination of its cDNA sequence and identification of a mutation causing alpha-mannosidosis in Persian cats, *Biochem J* 328 (Pt 3):863, 1997.
10. Bergsma DR, Brown KS: White fur, blue eyes, and deafness in the domestic cat, *J Hered* 62:171, 1971.
11. Bighignoli B, Niini T, Grahn RA et al: Cytidine monophospho-N-acetylneuraminic acid hydroxylase (CMAH) mutations associated with the domestic cat AB blood group, *BMC Genet* 8:27, 2007.
12. Biller DS, Chew DJ, DiBartola SP: Polycystic kidney disease in a family of Persian cats, *J Am Vet Med Assoc* 196:1288, 1990.
13. Biller DS, DiBartola SP, Eaton KA et al: Inheritance of polycystic kidney disease in Persian cats, *J Hered* 87:1, 1996.
14. Bradbury AM, Morrison NE, Hwang M et al: Neurodegenerative lysosomal storage disease in European Burmese cats with hexosaminidase beta-subunit deficiency, *Mol Genet Metab* 97:53, 2009.
15. Cannon MJ, MacKay AD, Barr FJ et al: Prevalence of polycystic kidney disease in Persian cats in the United Kingdom, *Vet Rec* 149:409, 2001.
16. Centerwall WR, Benirschke K: Animal model for the XXY Klinefelter's syndrome in man: tortoiseshell and calico male cats, *Am J Vet Res* 36:1275, 1975.
17. Chang J, Jung J, Oh S et al: Osteochondrodysplasia in three Scottish Fold cats, *J Vet Sci* 8:307, 2007.
18. Chu EHY, Thuline HC, Norby DE: Triploid-diploid chimerism in a male tortoiseshell cat, *Cytogenetics* 3:1, 1964.
19. Clavero S, Bishop DF, Giger U et al: Feline congenital erythropoietic porphyria: two homozygous UROS missense mutations cause the enzyme deficiency and porphyrin accumulation, *Mol Med* 16:381, 2010.
20. Clavero S, Bishop DF, Haskins ME et al: Feline acute intermittent porphyria: a phenocopy masquerading as an erythropoietic porphyria due to dominant and recessive hydroxymethylbilane synthase mutations, *Hum Mol Genet* 19:584, 2010.
21. Clavero S, Haskins M, Giger U et al: Molecular basis of acute intermittent porphyria in the cat, *Proc Adv Canine Feline Genomics Inherit Dis*, St Malo, France, 2008.
22. Crawley AC, Yogalingam G, Muller VJ et al: Two mutations within a feline mucopolysaccharidosis type VI colony cause three different clinical phenotypes, *J Clin Invest* 101:109, 1998.
23. De Maria R, Divari S, Bo S et al: Beta-galactosidase deficiency in a Korat cat: a new form of feline GM1-gangliosidosis, *Acta Neuropathol* 96:307, 1998.
24. Doncaster L: On the inheritance of tortoiseshell and related colours in cats, *Proc Cambridge Philosophical Soc* 13:35, 1904.
25. Drogemuller C, Rufenacht S, Wichert B et al: Mutations within the FGF5 gene are associated with hair length in cats, *Anim Genet* 38:218, 2007.
26. Eaton KA, Biller DS, DiBartola SP et al: Autosomal dominant polycystic kidney disease in Persian and Persian-cross cats, *Vet Pathol* 34:117, 1997.
27. Eizirik E, Yuhki N, Johnson WE et al: Molecular genetics and evolution of melanism in the cat family, *Curr Biol* 13:448, 2003.
28. Fries R, Heaney AM, Meurs KM: Prevalence of the myosin-binding protein C mutation in Maine Coon cats, *J Vet Intern Med* 22:893, 2008.
- 28a. Fyfe JC, Kurzhals RL, Hawkins MG et al: A complex rearrangement in GBE1 causes both perinatal hypoglycemic collapse and late-juvenile-onset neuromuscular degeneration in glycogen storage disease type IV of Norwegian forest cats, *Mol Genet Metab* 90:383, 2007.
29. Fyfe JC, Kurzhals RL, Lassaline ME et al: Molecular basis of feline beta-glucuronidase deficiency: an animal model of mucopolysaccharidosis VII, *Genomics* 58:121, 1999.
30. Fyfe JC, Menotti-Raymond M, David VA et al: An approximately 140-kb deletion associated with feline spinal muscular atrophy implies an essential LIX1 function for motor neuron survival, *Genome Res* 16:1084, 2006.
31. Gabor LJ, Canfield PJ, Malik R: Immunophenotypic and histological characterisation of 109 cases of feline lymphosarcoma, *Aust Vet J* 77:436, 1999.
32. Gabor LJ, Canfield PJ, Malik R: Haematological and biochemical findings in cats in Australia with lymphosarcoma, *Aust Vet J* 78:456, 2000.
33. Gabor LJ, Malik R, Canfield PJ: Clinical and anatomical features of lymphosarcoma in 118 cats, *Aust Vet J* 76:725, 1998.
34. Gandolfi B, Bach L, Beresford L et al: Off with the gloves: mutation in KIT implicated for the unique white spotting phenotype of Birman cats, *submitted for publication*, 2011.
35. Gandolfi B, Outerbridge C, Beresford L et al: The naked truth: Sphynx and Devon Rex cat breed mutations in KRT71, *Mamm Genome* 21:509, 2010.
36. The Governing Council of the Cat Fancy (GCCF): <http://www.gccfcats.org>. Accessed June 22, 2011.
37. Geisen V, Weber K, Hartmann K: Vitamin D-dependent hereditary rickets type I in a cat, *J Vet Intern Med* 23:196, 2009.
38. Ginzinger DG, Lewis ME, Ma Y et al: A mutation in the lipoprotein lipase gene is the molecular basis of chylomicronemia in a colony of domestic cats, *J Clin Invest* 97:1257, 1996.
39. Goldstein R, Narala S, Sabet N et al: Primary hyperoxaluria in cats caused by a mutation in the feline GRHPR gene, *J Hered* 100:S2, 2009.
40. Goree M, Catalfamo JL, Aber S et al: Characterization of the mutations causing hemophilia B in 2 domestic cats, *J Vet Intern Med* 19:200, 2005.
41. Gough A, Thomas A: *Breed predispositions to disease in dogs and cats*, ed 2, Oxford, England, 2010, Wiley-Blackwell.
42. Grahn R, Ellis M, Grahn J et al: No bones about it! A novel CYP27B1 mutation results in feline vitamin D-dependent Rickets Type I (VDDR-1), *J Feline Med Surg*, in press, 2012.
43. Gregson NM, Ishmael J: Diploid triploid chimerism in three tortoiseshell cats, *Res Vet Sci* 12:275, 1971.
44. Gundler S, Tidholm A, Haggstrom J: Prevalence of myocardial hypertrophy in a population of asymptomatic Swedish Maine coon cats, *Acta Vet Scand* 50:22, 2008.

45. He X, Li CM, Simonaro CM et al: Identification and characterization of the molecular lesion causing mucopolysaccharidosis type I in cats, *Mol Genet Metab* 67:106, 1999.
46. Ibsen HL: Tricolor inheritance. III. Tortoiseshell cats, *Genetics* 1, 1916.
47. Imes DL, Geary LA, Grahn RA et al: Albinism in the domestic cat (*Felis catus*) is associated with a tyrosinase (TYR) mutation, *Anim Genet* 37:175, 2006.
48. Ishida Y, David VA, Eizirik E et al: A homozygous single-base deletion in MLPH causes the dilute coat color phenotype in the domestic cat, *Genomics* 88:698, 2006.
49. Ishihara T: Cytological studies on tortoiseshell male cats, *Cytologia* 21: 391, 1956.
50. Johnson WE, Eizirik E, Pecon-Slattery J et al: The late Miocene radiation of modern Felidae: a genetic assessment, *Science* 311:73, 2006.
51. Kanae Y, Endoh D, Yamato O et al: Nonsense mutation of feline beta-hexosaminidase beta-subunit (HEXB) gene causing Sandhoff disease in a family of Japanese domestic cats, *Res Vet Sci* 82:54, 2007.
52. Kehler JS, David VA, Schaffer AA et al: Four independent mutations in the feline fibroblast growth factor 5 gene determine the long-haired phenotype in domestic cats, *J Hered* 98:555, 2007.
53. Kittleson MD, Meurs KM, Munro MJ et al: Familial hypertrophic cardiomyopathy in maine coon cats: an animal model of human disease, *Circulation* 99:3172, 1999.
54. Kohn B, Fumi C: Clinical course of pyruvate kinase deficiency in Abyssinian and Somali cats, *J Feline Med Surg* 10:145, 2008.
55. Kosowska B, Januszewski A, Tokarska M et al: Cytogenetic and histologic studies of tortoiseshell cats, *Med Weter* 57:475, 2001.
56. Kuiper H, Hewicker-Trautwein M, Distl O: [Cytogenetic and histologic examination of four tortoiseshell cats], *Dtsch Tierarztl Wochenschr* 110:457, 2003.
57. Kunzel W, Breit S, Oppel M: Morphometric investigations of breed-specific features in feline skulls and considerations on their functional implications, *Anat Histol Embryol* 32:218, 2003.
58. Lettice LA, Hill AE, Devenney PS et al: Point mutations in a distant sonic hedgehog cis-regulator generate a variable regulatory output responsible for preaxial polydactyly, *Hum Mol Genet* 17:978, 2008.
59. Lewis T, Rusbridge C, Knowler P et al: Heritability of syringomyelia in Cavalier King Charles spaniels, *Vet J* 183:345, 2010.
60. Li X, Li W, Wang H et al: Cats lack a sweet taste receptor, *J Nutr* 136:1932S, 2006.
61. Li X, Li W, Wang H et al: Pseudogenization of a sweet-receptor gene accounts for cats' indifference toward sugar, *PLoS Genet* 1:27, 2005.
62. Little CC: Colour inheritance in cats, with special reference to colours, black, yellow and tortoiseshell, *J Genet* 8:279, 1919.
63. Louwerens M, London CA, Pedersen NC et al: Feline lymphoma in the post-feline leukemia virus era, *J Vet Intern Med* 19:329, 2005.
64. Lyons LA, Biller DS, Erdman CA et al: Feline polycystic kidney disease mutation identified in PKD1, *J Am Soc Nephrol* 15:2548, 2004.
65. Lyons LA, Foe IT, Rah HC et al: Chocolate coated cats: TYRP1 mutations for brown color in domestic cats, *Mamm Genome* 16:356, 2005.
66. Lyons LA, Imes DL, Rah HC et al: Tyrosinase mutations associated with Siamese and Burmese patterns in the domestic cat (*Felis catus*), *Anim Genet* 36:119, 2005.
67. Malik R, Allan GS, Howlett CR et al: Osteochondrodysplasia in Scottish Fold cats, *Aust Vet J* 77:85, 1999.
68. Martin DR, Cox NR, Morrison NE et al: Mutation of the GM2 activator protein in a feline model of GM2 gangliosidosis, *Acta Neuropathol* 110:443, 2005.
69. Martin DR, Krum BK, Varadarajan GS et al: An inversion of 25 base pairs causes feline GM2 gangliosidosis variant, *Exp Neurol* 187:30, 2004.
70. Mazrier H, Van Hoeven M, Wang P et al: Inheritance, biochemical abnormalities, and clinical features of feline mucolipidosis II: the first animal model of human I-cell disease, *J Hered* 94:363, 2003.
71. Menotti-Raymond M, David VA, Pflueger S et al: Widespread retinal degenerative disease mutation (rdAc) discovered among a large number of popular cat breeds, *Vet J* 186:32, 2010.
72. Menotti-Raymond M, David VA, Schaffer AA et al: Mutation in CEP290 discovered for cat model of human retinal degeneration, *J Hered* 98:211, 2007.
73. Menotti-Raymond M, Deckman K, David V et al: Mutation discovered in a feline model of human congenital retinal blinding disease, *Invest Ophthalmol Vis Sci* 51:2852, 2010.
74. Meurs KM, Norgard MM, Ederer MM et al: A substitution mutation in the myosin binding protein C gene in ragdoll hypertrophic cardiomyopathy, *Genomics* 90:261, 2007.
75. Meurs KM, Sanchez X, David RM et al: A cardiac myosin binding protein C mutation in the Maine Coon cat with familial hypertrophic cardiomyopathy, *Hum Mol Genet* 14:3587, 2005.
76. Muldoon LL, Neuwelt EA, Pagel MA et al: Characterization of the molecular defect in a feline model for type II GM2-gangliosidosis (Sandhoff disease), *Am J Pathol* 144:1109, 1994.
77. Nakata N, Wang Y, Bhatt S: Trends in prenatal screening and diagnostic testing among women referred for advanced maternal age, *Prenat Diagn* 3:198, 2010.
78. Orioli I, Castilla E, Scarano G et al: Effect of paternal age in achondroplasia, thanatophoric dysplasia, and osteogenesis imperfecta, *Am J Med Genet* 59:209, 1995.
79. Paige CF, Abbott JA, Elvinger F et al: Prevalence of cardiomyopathy in apparently healthy cats, *J Am Vet Med Assoc* 234:1398, 2009.
80. Partington BP, Williams JF, Pechman RD et al: What is your diagnosis? Scottish Fold osteodystrophy, *J Am Vet Med Assoc* 209:1235, 1996.
81. Peterschmitt M, Grain F, Arnaud B et al: Mutation in the melanocortin 1 receptor is associated with amber colour in the Norwegian Forest Cat, *Anim Genet* 40:547, 2009.
82. Pion P, Kittleson M, Rogers Q et al: Taurine deficiency myocardial failure in the domestic cat, *Prog Clin Biol Res* 351:423, 1990.
83. Pyle RL, Patterson DF, Hare WCD et al: XXY sex chromosome constitution in a Himalayan cat with tortoiseshell points, *J Hered* 63:220, 1971.
84. Ripoll Vera T, Montserrat Iglesias L, Hermida Prieto M et al: The R820W mutation in the MYBPC3 gene, associated with hypertrophic cardiomyopathy in cats, causes hypertrophic cardiomyopathy and left ventricular non-compaction in humans, *Int J Cardiol* 145(2):405, 2010.
85. Robinson R: The rex mutants of the domestic cat, *Genetica* 42:466, 1971.
86. Robinson R: The Canadian hairless of Sphinx cat, *J Hered* 64:47, 1973.
87. Robinson R: Expressivity of the Manx gene in cats, *J Hered* 84:170, 1993.
88. Sampedrano C, Chetboul V, Mary J et al: Prospective echocardiographic and tissue Doppler imaging screening of a population of Maine Coon cats tested for the A31P mutation in the myosin-binding protein C gene: a specific analysis of the heterozygous status, *J Vet Intern Med* 23:91, 2009.
89. Schlueter C, Budras K, Ludewig E et al: Brachycephalic feline noses: CT and anatomical study of the relationship between head conformation and the nasolacrimal drainage system, *J Feline Med Surg* 11:891, 2009.
90. Schmidt-Kuntzel A, Eizirik E, O'Brien SJ et al: Tyrosinase and tyrosinase related protein 1 alleles specify domestic cat coat color phenotypes of the albino and brown loci, *J Hered* 96:289, 2005.
91. Somers K, Royals M, Carstea E et al: Mutation analysis of feline Niemann-Pick C1 disease, *Mol Genet Metab* 79:99, 2003.

92. Takanosu M, Takanosu T, Suzuki H et al: Incomplete dominant osteochondrodysplasia in heterozygous Scottish Fold cats, *J Small Anim Pract* 49:197, 2008.
93. Thomson PC, Wilson BJ, Wade CM et al: The utility of estimated breeding values for inherited disorders of dogs, *Vet J* 183:243, 2009.
94. Thuline HC: Male tortoiseshell, chimerism and true hermaphroditism, *J Cat Genet* 4:2, 1964.
95. TICA: The International Cat Association, 2010. <http://www.tica.org/>. Accessed June 22, 2011.
96. Tsoutsman T, Bagnall R, Semsarian C: Impact of multiple gene mutations in determining the severity of cardiomyopathy and heart failure, *Clin Exp Pharmacol Physiol* 35:1349, 2008.
97. Valayannopoulos V, Nicely H, Harmatz P et al: Mucopolysaccharidosis VI, *Orphanet J Rare Dis* 5:1, 2010.
98. Wess G, Schinner C, Weber K et al: Association of A31P and A74T polymorphisms in the myosin binding protein C3 gene and hypertrophic cardiomyopathy in Maine Coon and other breed cats, *J Vet Intern Med* 24:527, 2010.
99. Wilson TG, Kane F: Congenital deafness in white cats, *Acta Otolaryngolica* 50:269, 1959.
100. Winand NJ, Edwards M, Pradhan D et al: Deletion of the dystrophin muscle promoter in feline muscular dystrophy, *Neuromuscul Disord* 4:433, 1994.
101. Yogalingam G, Hopwood JJ, Crawley A et al: Mild feline mucopolysaccharidosis type VI. Identification of an N-acetylgalactosamine-4-sulfatase mutation causing instability and increased specific activity, *J Biol Chem* 273:13421, 1998.
102. Yogalingam G, Litjens T, Bielicki J et al: Feline mucopolysaccharidosis type VI. Characterization of recombinant N-acetylgalactosamine 4-sulfatase and identification of a mutation causing the disease, *J Biol Chem* 271:27259, 1996.