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CLINICAL REVIEW

DNA MUTATIONS OF THE CAT
The good, the bad and the ugly

Leslie A Lyons

Practical relevance: The health of the cat is a complex interaction between its environment (nurture) and its genetics (nature). Over 70 genetic mutations (variants) have been defined in the cat, many involving diseases, structural abnormalities and clinically relevant health concerns. As more of the cat's genome is deciphered, less commonly will the term 'idiopathic' be used regarding the diagnosis of diseases and unique health conditions. State-of-the-art health care will include DNA profiling of the individual cat, and perhaps its tumor, to establish the best treatment approaches. Genetic testing and eventually whole genome sequencing should become routine diagnostics for feline health care.

Global importance: Cat breeds have disseminated around the world. Thus, practitioners should be aware of the breeds common to their region and the mutations found in those regional populations. Specific random-bred populations can also have defined genetic characteristics and mutations.

Audience: This review of 'the good, the bad and the ugly' DNA variants provides the current state of knowledge for genetic testing and genetic health management for cats. It is aimed at feline and general practitioners wanting to update and review the basics of genetics, what tests are available for cats and sources for genetic testing. The tables are intended to be used as references in the clinic. Practitioners with a high proportion of cat breeder clientele will especially benefit from the review.

Evidence base: The data presented is extracted from peer-reviewed publications pertaining to mutation identification, and relevant articles concerning the heritable trait and/or disease. The author also draws upon personal experience and expertise in feline genetics.

Defining mutations

The word 'mutation' generally conjures up negative associations, such as Frankenstein's monster or the X-Men. However, just as Frankenstein's monster was misunderstood, and the X-Men can use their powers for good or evil, misconceptions surround DNA mutations found in the mammalian genome, including those of the domestic cat. The definition of mutation is: 'a major change; a significant and basic alteration' (Webster's Third New International Dictionary). In the context of heredity, this change implies a difference from the 'wild type' – the typical form of an organism as ordinarily encountered in nature. Note that 'mutation' and 'typical' do not infer good or bad, and 'ordinarily' applies to the current space and time. Indeed, to remove negative connotations, the current standard is to use the term 'variant' instead of 'mutation' when referring to changes in DNA.

To date, over 40 genes with approximately 70 DNA mutations (variants) have been documented to cause phenotypic, disease or blood type variations in the domestic cat.

The wild type cat is a brown mackerel tabby with moderate body and facial conformation (Figure 1). As species evolve, mutation to DNA occurs, causing DNA variants, and the frequencies of those variants in the population change due to natural and artificial selection, migrations, popular sires and founder individuals. Over time, the extraordinary can become the ordinary. For example, the current 'ordinary' Persian cat has a highly brachycephalic head type. However, 100 years ago, Persians were just longhaired cats with a moderately normal face, which would currently be the extraordinary atypical! Although the change in the Persian head structure has been accomplished by artificial selection, natural selection changes the wild type over time as well, especially in relation to genes and alleles that affect fitness (ie, health).

Fitness is reduced any time a cat cannot reproduce, has lowered fecundity and/or a shortened reproductive lifespan. Barring accidents and traumas (eg, hit-by-car or eaten-by-coyote) the standard non-pedigreed cat, which has access to outdoors, should live at least 12 years

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Single DNA variant effects on coloration in cats

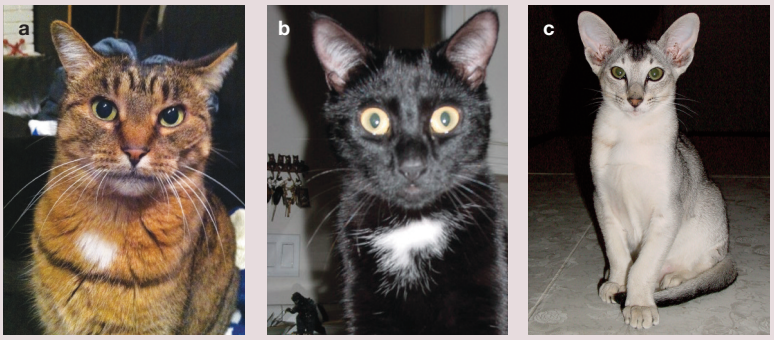

Figure 1 (a) The brown mackerel tabby constitutes the wild type cat. The brown fur is an optical illusion, being banded with black (eumelanin) and yellow pigment (pheomelanin). Wild type alleles of genes can be dominant or recessive and are designated with a superscript '+'. Alleles at the different color loci can be represented for the brown mackerel tabby as: A^+ –, B^+ –, C^+ –, D^+ –, E^+ –, i^+i^+, L^+ –, o^+o^+, s^+s^+, T^m –, *titi*, w^+w^+. (b) One variant in the locus *Agouti*, the non-agouti allele, *a*, can make the fur appear solid, although all the other alleles are the same. Only the pheomelanin is replaced with black pigment in the solid black cat, which still has tabby markings. The black cat can be represented as: *aa*, B^+ –, C^+ –, D^+ –, E^+ –, i^+i^+, L^+ –, o^+o^+, s^+s^+, T^m –, *titi*, w^+w^+. (c) This silver Oriental Shorthair kitten displays the effect of the *Inhibitor* gene that removes pheomelanin from the coat and the effect of the *Ticked* allele that epistatically suppresses *Tabby* markings: A^+ –, B^+ –, C^+ –, D^+ –, E^+ –, *I* –, L^+ –, o^+o^+, s^+s^+,Ti^a –, w^+w^+. (Epistasis is a phenomenon whereby one gene locus masks or modifies the phenotype of a second gene locus)

and succumb to renal disease, hyperthyroidism or lymphosarcoma. Younger cats with morbidities or mortalities that should generally take the older and the weaker individuals, likely have alleles that are compromising their fitness, making them 'susceptible' to disease. Conversely, many cats live well into their teens; their genomes likely possess DNA variants that improve their overall fitness, enhancing their 'resistance' to disease.

Feral cats that live in more natural, and often more harsh, environments obtain DNA variants at the same rate as non-pedigreed and pedigreed cats, but often have a shorter lifespan. Besides the cat–cat competition and traumas more likely sustained in the open environment by a feral cat, DNA variants conferring poor fitness will lower the reproductive capabilities of a given cat. Therefore, variants that reduce fitness will more likely be maintained at a lower frequency in the feral population than in our health-managed non-pedigreed and fancy breed cats. In other words, health management allows genes conferring poorer fitness to survive and propagate in the species.

Overall, most variants are neutral and many are good. DNA variants support a species' evolution by conferring advantages to different selection pressures. A population needs variation so that given individuals can fend off viruses and other infections that are the likely cause of early death in cats, allowing them to propagate and contribute to a species that is slightly more evolved, having better fitness for the current environment. As discussed below, many 'good' DNA variants are in fact just aesthetically pleasing and confer beauty and uniqueness to individual cats and their various breeds. Like any species, cats also have some very 'bad' and 'ugly' DNA variants.

Overall, most DNA variants are neutral and many are good – conferring advantages to different selection pressures.

The 'good' cat variants – variation humans positively select in cats

To date, over 40 genes with approximately 70 DNA variants have been documented to cause phenotypic, disease or blood type variations in the domestic cat (see reviews)[1–3]. The clinical descriptions and phenotypes of each of these diseases and traits have been curated at the Online Mendelian Inheritance in Animals (OMIA) website (omia.angis.org.au), which provides an invaluable resource comparison of phenotypes across 216 animal species.[4] The 26 genes in Table 1 are often under positive selection in cats, particularly breeds; however, not all of the variants may be considered 'good' by current standards (see later).

Once cats became domesticated, some of the first noticeable genetic alterations conferred phenotypic variations in fur length, fur type, coat colors and coat patterns. Most of the phenotypic genes and loci that affect the appearance of a cat (Table 1) can be remembered simply by referring to letters of the alphabet.

Genes, loci and alleles

- **A gene** for a trait is made up of DNA, which makes a protein that gives rise (directly or indirectly) to the trait of interest.
- **A locus** refers to the place on the chromosome, within the DNA sequence, where the gene is localized. The locus in the cat genome that controls when the yellow and black pigment is turned on and off during the production of a hair is known as *Agouti*.
- **An allele** is a given DNA sequence for a gene. The normal allele for *Agouti* was defined as 'A^+' and the mutant was defined as '*a*'. Lower case letters imply recessive alleles, upper case implies dominant alleles. Thus, to get a non-agouti (solid) cat, there has to be two copies of the mutant allele, '*aa*'.

Once we have learned what protein is produced by a given gene at a specific locus, the gene name is then redefined after a function of the protein. *Agouti* is defined by the gene termed *agouti-signaling protein*, which is abbreviated to *ASIP*. In cats, *ASIP* has two alleles, A^+ and *a*. Alleles, loci and gene names are written in italics but the actual protein is written in roman (normal) font. Additional alleles at a gene can be indicated by other superscript letters that help define the effect. A^{Pbe}, for example, indicates that this is the *Agouti* allele from the Leopard Cat (*Prionailurus bengalensis* [Pbe]), which is segregating in the Bengal cat breed.

Table 1 Phenotypic traits of the domestic cat conferred by DNA variants

Locus (Alleles) OMIA entry link	MOI*	Phenotype	Gene	Gene name	Mutation
Agouti (A^+, *a*)[5] 000201-9685	AR	**Banded fur to solid**	*ASIP*	*Agouti-signaling protein*	c.122_123delCA
Brown (B^+, *b*, b^l)[6,7] 001249-9685	AR	**Brown, light brown color variants**	*TYRP1*	*Tyrosinase-related protein*	b = -5IVS6 b^l = c.298C>T
Color (C^+, C^b, C^s, *c*)[7–9] 000202-9685	AR	**Burmese, Siamese color pattern, full albino**	*TYR*	*Tyrosinase*	c^b = c.715G>T c^s = c.940G>A c = c.975delC
Dilution (D^+, *d*)[10] 000206-9685	AR	**Black to grey/blue, orange to cream**	*MLPH*	*Melanophilin*	c.83delT
Dwarfism 000299-9685	AD	**Shortening of long bones**	unknown	unknown	unknown
Extension (E^+, *e*) – *Amber*[11] 001199-9685	AR	**Brown/red color variant**	*MC1R*	*Melanocortin receptor 1*	c.250G>A
Fold (*Fd*, fd^+) 000319-9685	AD	**Ventral ear fold**	unpublished	unpublished	unpublished
Gloves (G^+, *g*)[12] 001580-9685	AR	**White feet**	*KIT*	*KIT*	c.1035_1036delinsCA
Hairless (Hr^+, *hr*)[13]	AR	**Atrichia**	*KRT71*	*Keratin 71*	c.816+1G>A
Inhibitor (*I*, i^+) 001584-9685	AD	**Absence of pheomelanin**	unknown	unknown	unknown
Japanese Bobtail (*J*, j^+)	AD	**Kinked tail**	unknown	unknown	unknown
Kurl (*K*, k^+) 000244-9685	AD	**Rostral curled pinnae**	unknown	unknown	unknown
LaPerm 000245-9685	AD	**Curly hair coat**	unknown	unknown	unknown
Longhair (L^+, *l*)[14,15] 000439-9685	AR	**Long fur**	*FGF5*	*Fibroblast growth factor 5*	c.356_367insT c.406C>T c.474delT c.475A>C
Tailless (Manx) (*M*, m^+)[16] 000975-9685	AD	**Absent/short tail**	*TBOX*	*T-box*	c.998delT c.1169delC c.1199delC c.998_1014dup17delGCC
Orange (*O*, o^+) 001201-9685	X-linked	**Change in pigment hue**	unknown	unknown	unknown
Peterbald 001866-9685	AD	**Hairless, brush coat**	unknown	unknown	unknown
Polydactyla (*Pd*, pd^+)[17] 000810-9685	AD	**Extra toes**	*SHH*	*Sonic hedgehog*	c.479A>G c.257G>C c.481A>T
Rexing (R^+, *r*)[18] 001684-9685	AR	**Curly hair coat**	*LPAR6*	*Lysophosphatidic acid receptor 6*	c.250_253delTTTG
Rexing (Re^+, *re*)[13] 001581-9685	AR	**Curly hair coat**	*KRT71*	*Keratin 71*	c.1108-4_1184del, c.1184_1185insAGTTGGAG c.1196insT
Rexing (R^S, r^{s+})[19] 001712-9685	AD	**Curly hair coat**	*KRT71*	*Keratin 71*	c.445-1G>C
Spotting (*S*, s^+)[20] 000214-9685	Co-D	**Bicolor/Van white**	*KIT*	*KIT*	7125ins FERV1 element
Tabby (T^M, t^b)[21] 001429-9685	AR	**Blotched/classic pattern**	*TAQPEP*	*Transmembrane aminopeptidase Q*	c.176C>A c.416C>A c.682C>A c.2522G>A
Ticked (Ti^a, *ti*) 001484-9685	AD	**No tabby pattern**	unknown	unknown	unknown
White (*W*, w^+)[20] 000209-9685	AD	**Loss of pigmentation**	*KIT*	*KIT*	FERV1 LTR ins
Wide-band	AR?	**Length of pheomelanin band in hair**	unknown	unknown	unknown

*Mode of inheritance of the non-wild type variant. '+' implies the wild type allele when known. In reference to the mutant allele, AD = autosomal dominant, AR = autosomal recessive, co-D = co-dominant.
OMIA: Online Mendelian Inheritance in Animals (omia.angis.org.au) entries provide links to citations and clinical descriptions of the phenotypes and the diseases. Listed citations are for the causative variant discovery

Longhair of domestic cat breeds

Figure 2 **A variety of cats have long fur, but different causal variants in the gene *fibroblast growth factor 5* (*FGF5*) exist. Ragdolls (a) have a variant that likely derived in the USA; Persians (b) have the ancient variant that derived from the Near and Middle East and is common to most longhaired breeds; Norwegian Forest Cats (c) have a variant common to Nordic race cats; and Maine Coons (d) may have a fourth variant, likely also derived in the USA. The Ragdoll and Norwegian Forest Cat are also bicolor at the *Spotting* locus, *Ss*.** *Images courtesy of Animal Photography*

Mostly these loci were named after traits that were first discovered in the domestic mouse, before anything was known of the genes and the proteins they produced.[22] *A* is for *Agouti*, *B* is for *Brown*, *C* is for *Color*, *D* is for *Dense*, *E* is for *Extension* (amber), and so forth. The *Color* (aka *Chinchilla*) locus was named after a mouse phenotype that presented similarly to the coloration of the Siamese cat, having color only on its cooler extremities. The *Dense* (*Dilute*) locus affects the amount and placement of pigment in the hair shaft, giving the illusion that a cat is grey or blue. Also known as dilution, blue cats only have black pigment, but the refractive qualities of the hair shaft cause the illusion of a lighter pigment.[23,24] The coat color variants are common to all cats and are appropriate for genetic typing in all breeds and populations.

Together with *I* for *Inhibitor*, *L* for *Longhair* (*fur*), *S* for *Spotting*, *T* for *Tabby*, *O* for *Orange*, and *W* for *White*, these loci (*A–E*, *I*, *L*, *S*, *T*, *O* and *W*) control the major phenotypic traits of cats that appeared before the development of cat breeds.

Many early geneticists studied the coat colors of cats to understand basic inheritance patterns. *Orange* is defined by a yet unknown gene on the X chromosome in cats.[25,26] Because *Orange* is sex-linked, its inheritance pattern is very different between males and females, males being more likely to be orange since they have only one X chromosome. *Orange* was one of the first loci to be genetically mapped to a specific chromosome,[27–30] for any species! *Longhair* has four different variants that have likely occurred in different regions of the world and are prevalent in certain breeds to greater or lesser degrees (Figure 2).[13,14] A gene for tabby patterns has long been known, but it was recently shown that another gene controls the expression of the *Tabby* locus and hence the tabby phenotype (Figure 3).[21,31] The *Tabby* locus (*TAQPEP* gene) controls the blotched/classic tabby pattern (t^b). However, a second gene locus, dubbed *Ticked*, is now considered to turn tabby patterns on and off. The historically known ticked tabby phenotype (tabby Abyssinian, T^a) is at this

Tabby patterns of domestic cat breeds

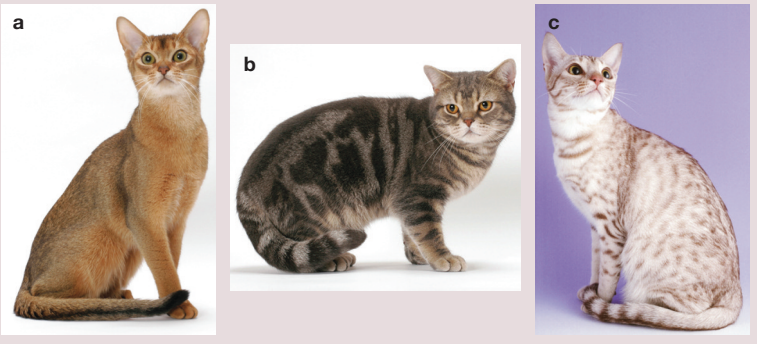

Figure 3 **Tabby patterns of cats are complex. The Abyssinian (a) displays a variant at likely the *Ticked* locus (Ti^a) that turns off all patterning of the *Tabby* locus (tabby aby or ticked tabby), no matter what allele is present at *Tabby*. The American Shorthair (b) has the allele at the *Ticked* locus (*ti*) that allows the display of the two recessive blotched (t^b) alleles at the *Tabby* locus to produce a classic or blotched tabby. The Ocicat (c) has the allele at the *Ticked* locus (*ti*) that allows the display of the alleles at the *Tabby* locus, which are likely modified by other genes to form the spots. The modifier genes are not clearly resolved.** *Images courtesy of Animal Photography*

second locus, the gene for which is not yet identified. The actual pattern is then controlled by *TAQPEP* (*Tabby*) and other modifier genes as well.

Spotting and *White* are two very interesting and complex loci. The gene was recently identified, demonstrating that full white and bicolor white are alleles at the oncogene called *KIT*.[20] *KIT* is also responsible for the gloving of the white feet in Birmans, thus comprising at least three alleles that confer white fur.[12] However, white spotting is very complex in most domesticated species; a good example is provided by horse spotting genes and their alleles.[32,33] Thus, *KIT* may not explain all white spotting in cats; nor has the association with deafness been elucidated.[34–36] White spotting is also associated with the domestication of foxes and is likely associated with other domesticated species.[37] The first sign of domestication of the wild type cat in Figure 1 is the white spot on the neck.

In cats, the *Spotting* locus, now known to be *KIT*, has at least three alleles, wild type and *spotting*.[38] One copy of the *S* allele appears to make a bicolor cat (Figure 2), while two copies, *SS*, appear to produce a high white, 'Van', patterned cat. However, other alleles may be present, as white spotting patterns in the Ragdoll breed are difficult to predict, even though they appear similar to those seen in other breeds. For example, the white 'mittens' of some Ragdolls are not controlled by the same DNA variants as the white 'gloves' in the Birman.[12] The control of white spots on the neck and belly is also unknown, although many of these presentations could be due to random midline closure defects of melanocyte migration.

Thus, many of the 'good' DNA variants of cats confer their aesthetical qualities and many more recent DNA variants have been identified since cat breeding became established. Newer variants, such as many of the fur types, are unique and breed-defining. Some of the earliest phenotypes noted for a breed were the curly coats of the Cornish Rex[39] and Devon Rex,[40] which were among the first novelty breeds.[41,42] More recent breed-defining fur type variants that are scientifically documented include hairless cats (Sphynx and Peterbalds)[43,44] and the highly curled Selkirk Rex.[45] Other rare breeds, such as LaPerm (tica.org/cat-breeds/item/228) and Tennessee Rex (tennesseerex.com) have not been defined but have recognized curly-coated variants.

Many 'good' DNA variants are just aesthetically pleasing and confer beauty and uniqueness to individual cats and their various breeds.

'Good' variants of concern

So which of the DNA variants listed in Table 1 might we not consider 'good' by current cat breeding standards?

- Many of the coat color variants, such as *White* and *Spotting*, may be detrimental in the feral state, especially since they have not been documented in wildcats (*Felis silvestris*).
- Dominant *White* is associated with deafness and increased risk of melanoma due to depigmentation and ultraviolet exposure.[34–36]
- The Manx DNA alterations are lethal in utero in the homozygous state and many Manx cats have issues with lameness, incontinence and constipation.[46–49] The discovery of the *Tailless* variants has also revealed that Japanese Bobtails[50] do not have DNA changes in the same gene and that the Pixiebob breed has Manx and Japanese Bobtail genetic contributions.[15]
- Many argue that the hairless phenotypes are 'too unnatural' for a cat and they can suffer from potential hypothermia and sunburn.
- Well known health concerns surround the ear fold phenotype of the Scottish Fold (see Figure 6a), which is associated with osteochondrodysplasia.[51] While many breeders seem to think that osteochrondrodysplasia occurs only in the homozygous cat, it is likely that some disease in heterozygotes manifests subclinically.
- Dwarfism is another controversial phenotype, propagated as the Munchkin cat breed. However, the dwarfism gene and the DNA variant have not been scientifically documented and health concerns not yet identified.

Deciphering the gene alleles associated with Scottish Folds and dominant *White* cats will likely help us understand the basic biology of the genes and the role of genetic modifiers that influence the undesired and linked health concerns.

How does this knowledge support cat health?

Knowledge and understanding of the mode of inheritance and effect of the aesthetic, phenotypic alleles can support cat health in an indirect manner, through population management. If breeders can be counselled on breeding schemes that will produce more of the color and fur type varieties that are preferred and less that are undesired, fewer unwanted cats are produced. Fewer unwanted cats reduce cat overpopulation and the likelihood that individual cats representing breeds will be relegated to animal shelters. In addition, if a breeder has more desired cats and fewer surplus cats, more time, energy and precious funds can be designated to the health care of the desired cats. Importantly, the reduction of breeding cattery size inherently reduces stress and stress-associated health issues, such as upper respiratory diseases, urinary tract diseases and feline infectious peritonitis. Thus, correct genetic management of a simple coat color trait may indirectly improve the health of the entire cattery.

The 'bad' cat variants – variation humans negatively select in cats

Although current genetics focuses on DNA alterations that affect specific genes, some of the earliest genetic testing for any species involved the examination of the full set of chromosomes (karyotype) of an individual to determine whether the normal number and arrangement of chromosomes were present (Figure 4). Sex chromosome aneuploidies (losses), and trisomies of small acrocentric chromosomes (chromosomes with no short [p] arm), are typically associated with decreased fertility and syndromes that display distinct morphological abnormalities. Turner's syndrome (XO), Klinefelter's syndrome (XXY)[52,53] and chimerisms have been documented in the domestic cat. Because the cat has a highly recognizable X-linked trait,[27–30] *Orange*, tortoiseshell and calico (tortoiseshell and white) male cats were the first feline suspects of sex chromosomal abnormalities. Karyotypic studies of male tortoiseshell cats have shown that they are often mosaics, or chimeras, being XX/XY in all or some tissues.[28,52–59]

Although gene-based assays are common methods to determine if a cat with ambiguous genitalia[60] or a poor reproductive history has a chromosomal abnormality, karyotypes are still often performed. Domestic cats have an easily distinguishable karyotype (see box).

The alignment of genes on chromosomes in cats is very similar to the genomic organization in humans.[64] Humans have their genes distributed onto 22 autosomes; therefore, only a small number of changes is required to rearrange the same genes onto 18 autosomes, as found in cats. However, although the cat genome is conserved to humans, certain well-known chromosomal abnormalities are not found (Figure 4). For example, an analog to Down's syndrome is not present in the cat since the genes found on human chromosome 21 are represented on the mid-sized metacenteric chromosome C2, which also has genes from human chromosome 3. A trisomy C2 would disrupt more genes than a trisomy 21 in humans; thus, in cats, more likely there is early fetal loss that is never detected.[65] The minor chromosomal differences that are cytogenetically detectable between a domestic cat and a Leopard Cat are likely the cause of fertility problems in the Bengal cat breed,[61,66] which is a hybrid between these two species.[67] Other significant chromosomal abnormalities causing common 'syndromes' are not well documented in the cat.

Several research and commercial laboratories can perform cat chromosomal analyses when provided with a living tissue, such as a skin biopsy for fibroblast culturing or whole blood for the analysis of white blood cells.

Genetic variants for routine screening

The first gene-specific DNA variants identified in cats were for gangliosidosis and muscular dystrophy; both discovered in 1994,[68,69] and both diseases that had well-defined phenotypes and known (candidate) genes with DNA alterations in humans. Most diseases are identified in pedigreed cats, which represent a small percentage of the cat population of the world, perhaps at most 10–15% in the USA.[70] The genetically characterized diseases and health concerns for breeds of domestic cats are presented in Table 2. Most of the identified disease tests in cats that are very specific to breeds and populations are available as commercial genetic tests offered by university and private laboratories (Table 3).

These are the DNA variants that should be monitored by cat breed registries and that veterinary practitioners should most familiarize themselves with, as they are useful diagnostically. Polycystic kidney disease (PKD), for example, is the most prevalent genetic disease in cats and an important diagnostic for early

Genetic testing is an effective preventative medicine tool and a potential ultimate cure through selective breeding.

Karyotype of the domestic cat

The karyotype of the domestic cat consists of 18 autosomal chromosomes and the XY sex chromosome pair, resulting in a 2N complement of 38 chromosomes for the cat genome[61] (Figure 4). Cat chromosomes are clearly defined by size; centromere position; distinctive giemsa banding patterns of the short (p) and long (q) arms of each chromosome; and the presence of only a few small acrocentric chromosomes. Although a sequential numbering system for the chromosomes has been suggested,[62] the historical classification of chromosomes into morphologic groups (A to F; Figure 4) has been retained for the cat: group A being large metacentrics; group B, large subtelomerics; group C, medium-size metacentrics; group D, small subtelomerics; group E, small metacentrics; and group F, small acrocentrics. The X chromosome is mid-sized and subtelomeric, similar to chromosome B4. As in most mammals, the Y chromosome is small and has few genes, but does possess regions that can pair with the X chromosome, forming pseudoautosomal regions.[63]

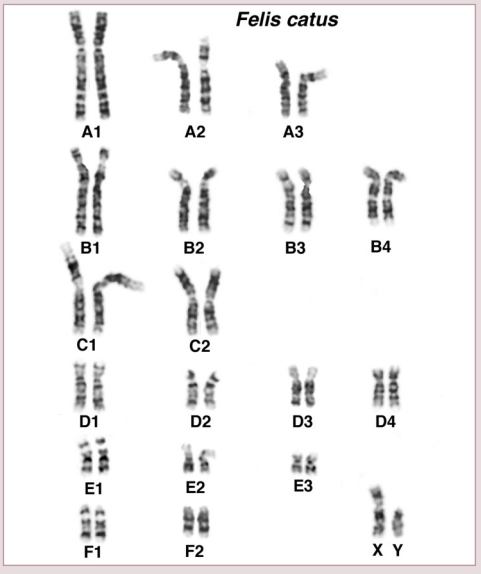

Figure 4 Chromosomes of the domestic cat. Giemsa banding (G-banding) helps to define cat chromosomes according to the positioning and thickness of the light and dark bands. Cat chromosomes can also be easily distinguished by size and shape. Cats have three large metacentric chromosomes (A1 to A3), four large subtelomeric chromosomes (B1 to B4), two medium-size metacentrics (C1 to C2), four small subtelomerics (D1 to D4), three small metacentrics (E1 to E3) and two small acrocentrics (F1 and F2). The X chromosome is mid-sized and subtelomeric, similar to chromosome B4. An X and a Y chromosome imply this cat is a male. *Karyotype courtesy of William Nash*

Table 2 Inherited diseases of domestic cats for which a commercial DNA test is available

Disease/trait (Alleles) OMIA entry link	MOI*	Phenotype	Gene	Gene name	Mutation
AB blood type (*A*$^+$, *b*)[71] 000119-9685	AR	Determines type B	*CMAH*	*Cytidine monophospho-N-acetylneuraminic acid hydroxylase*	c.1del-53_70 c.139G>A
Craniofacial defect	AR	Craniofacial defect	unpublished	unpublished	unpublished
Gangliosidosis 1[72] 000402-9685	AR	Lipid storage disorder (GM1)	*GLB1*	*Galactosidase, beta 1*	c.1457G>C
Gangliosidosis 2[69,73] 01462-0985	AR	Lipid storage disorder (GM2)	*HEXB*	*Hexominidase B*	c.1356del-1_8 c.1356_1362delGTTCTCA c.39delC
Glycogen storage disease IV[74] 000420-9685	AR	Glycogen storage disorder	*GBE1*	*Glycogen branching enzyme 1*	IVS11+1552_IVS12-1339 del6.2kb ins334 bp
Hypertrophic cardiomyopathy[75,76] 000515-9685	AD	Cardiac disease (HCM)	*MYBPC*	*Myosin binding protein C*	c.93G>C c.2460C>T
Hypokalemia[77] 001759-9685	AR	Potassium deficiency (HK)	*WNK4*	*WNK lysine deficient protein kinase 4*	c.2899C>T
Progressive retinal atrophy[78] 001244-9685	AR	Late-onset blindness (rdAC)	*CEP290*	*Centrosomal protein 290kDa*	IVS50 + 9T>G
Progressive retinal atrophy[79] 000881-9685	AD	Early-onset blindness (rdy)	*CRX*	*Cone-rod homeobox*	c.546delC
Polycystic kidney disease[80] 000807-9685	AD	Kidney cysts (PKD)	*PKD1*	*Polycystin 1*	c.10063C>A
Pyruvate kinase deficiency[81] 000844-9685	AR	Hemopathy (PK deficiency)	*PKLR*	*Pyruvate kinase, liver, RBC*	c.693+304G>A
Spinal muscular atrophy[82] 000939-9685	AR	Muscular atrophy (SMA)	*LIX1-LNPEP*	*Limb expression 1 homolog – leucyl/cystinyl aminopeptidase*	Partial gene deletions

*Mode of inheritance of the non-wild type variant. Not all transcripts for a given gene may have been discovered or well documented in the cat; mutations presented as interpreted from original publication. '+' implies the wild type allele when known. In reference to the mutant allele, AD = autosomal dominant, AR = autosomal recessive. OMIA: Online Mendelian Inheritance in Animals (omia.angis.org.au) entries provide links to citations and clinical descriptions of the phenotypes and the diseases. Listed citations are for the causative variant discovery

kidney disease (Figure 5). The prevalence of PKD in Persians was estimated at 30–38% worldwide, prior to the introduction of the genetic test.[83–85] Because of crossbreeding with Persians, many other breeds, such as the British Shorthair, American Shorthair, Selkirk Rex and Scottish Fold (Figure 6) also need to be screened for PKD.[86–88] The discovery of the hypokalemia DNA variant for Burmese cats reveals that a gene influencing overall potassium levels in cats can also influence blood pressure in humans.[89] By considering the breed relationships in Table 4, genetic health concerns across cat populations and breeds can be inferred due to inheritance ('identity by descent') via outcrossing.

Polycystic kidney disease (PKD) in the Persian cat

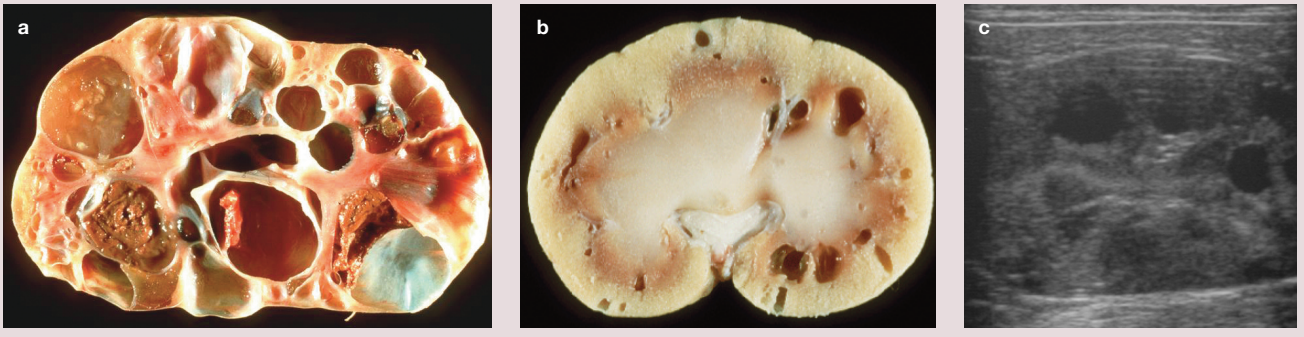

Figure 5 Severe (a) and mild (b) PKD. Cats can succumb to kidney failure when severe disease is present. Most cats have mild disease and will likely not succumb. (c) Ultrasound image of a cat with moderate to severe PKD. Any cat breeders outcrossing to Persians should also be concerned with PKD. *Images (a) and (b) courtesy of Steven DiBartola and (c) courtesy of David Biller*

Table 3 Laboratories performing DNA testing of domestic cats

Laboratory	Region	University research affiliate	ID	Cat tests*/ Disease	Color	Blood	Coat
Animal DNA Laboratory (Orivet Genetic Pet Care) animalsdna.com	Australia, New Zealand		Yes	8	4	Yes	Long
Animal Health Trust aht.org.uk	UK	Animal Health Trust	Yes	PKD	No	No	No
Antagene antagene.com	France		Yes	4	Color	Yes	No
BioAxis DNA Research Centre dnares.in	India		Yes	PKD	No	No	No
DNA Diagnostics Center dnacenter.com	USA		No	PKD	No	No	No
Genindexe genindexe.com	France		Yes	7	5	Yes	No
Genoscoper Laboratories genoscoper.com	Finland		Yes	7	Yes	Yes	Long
Gribbles Veterinary gribblesvets.com	Australia, New Zealand		No	PKD	No	No	No
IDEXX Laboratories idexx.ca	Canada		No	PK deficiency	No	No	No
Laboklin laboklin.de	Germany		Yes	9	5	Yes	Long
Langford Veterinary Services langfordvets.co.uk	UK	Bristol	Yes	10	8	Yes	Long
PennGen† research.vet.upenn.edu/penngen	USA	Pennsylvania	No	PK deficiency GSD	No	No	No
Progenus progenus.be	Belgium		Yes	7	6	No	Long
VHL Genetics vhlgenetics.com	Netherlands, Belgium, Germany		Yes	10	6	Yes	Long
NC State CVM Veterinary Genetics Laboratory ncstatevets.org/genetics	USA	North Carolina State	No	HCM	No	No	No
Veterinary Genetics Laboratory vgl.ucdavis.edu	USA	California, Davis	Yes	14	All	Yes	All
VetGen vetgen.com	USA	Michigan	Yes	No	Brown Dilute	No	Long
VetoGene vetogene.com	Italy	Milan	Yes	5	No	Yes	Long
Servicio de Genética ucm.es/genetvet	Spain	Madrid	Yes	8	Yes	No	Yes
Biofocus biofocus.de	Germany		Yes	7	Yes	Yes	No
Genefast genefast.com	Italy		Yes	No	Yes	No	No

*Tests refer to those listed in Tables 1 and 2. If a laboratory offers only one or two tests, those tests are listed, otherwise the number of tests offered for cats is presented. Polycystic kidney disease (PKD) and the hypertrophic cardiomyopathy (HCM) tests are the most popular cat offerings.
†PennGen also offers tests for diseases in Table 5 that are not of concern to the cat breeds or cat population in general. PK = pyruvate kinase, GSD = glycogen storage disease

Other DNA variants for which genetic tests are available

Some DNA variants have been found in individual cats of a certain breed, such as mucopolysaccharidosis type VI in the Siamese, but the variant is not of significant concern in the breed at large.[93,94] Table 5 lists DNA alterations identified in random-bred cats and disease-conferring variants that have not propagated within a breed. These genetic variants do not warrant 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.

Table 4 Genetic families of domestic cat breeds

Breed/family	Origin	Derived breed/grouping*
Abyssinian	India?	Somali
American Bobtail	Natural mutation	United States – random breds
American Curl	Natural mutation	United States – random breds
American Shorthair	United States	American Wirehair
American Wirehair	Natural mutation	American Shorthair
Australian Mist	Crossbreed hybrid	Burmese derived
Balinese	Variant	Colorpoint, Havana Brown, Javanese, Oriental, Siamese
Bengal	Species hybrid	Leopard Cat × Egyptian Mau and Abyssinian
Birman	Southeast Asia	
Bombay	Variant	Burmese, Singapura, Tonkinese
British Shorthair	Europe	Scottish Fold, Selkirk Rex
Burmese	Southeast Asia	Bombay, Singapura, Tonkinese
Burmilla	Crossbreed hybrid	Burmese, Persian
Chartreux	Europe	
Colorpoint Shorthair	Variant	Balinese, Havana Brown, Javanese, Oriental, Siamese
Cornish Rex	Natural mutation	United Kingdom – random breds
Devon Rex	Natural mutation	United Kingdom – random breds, Sphynx
Egyptian Mau	Mediterranean	
European	Europe	
Exotic	Variant	Persian
Havana Brown	Variant	Balinese, Colorpoint, Javanese, Oriental, Siamese
Japanese Bobtail	Founder	
Javanese	Variant	Balinese, Colorpoint, Havana Brown, Oriental, Siamese
Korat	Southeast Asia	
Kurilean Bobtail	Natural mutation	Eastern Russia, Kuril Islands
LaPerm	Natural mutation	United States – random breds
Maine Coon	United States	
Manx	Natural mutation	United Kingdom – random breds
Munchkin	Natural mutation	United States – random breds
Norwegian Forest Cat	Europe	
Ocicat	Crossbreed hybrid	Siamese × Abyssinian
Oriental	Variant	Balinese, Colorpoint, Havana Brown, Javanese, Siamese
Persian	Europe	Exotic
Peterbald	Mutation	Russian – random breds, Don Sphynx
Pixiebob	Crossbreed hybrid	Manx, Japanese Bobtail, United States – random breds
Ragdoll	United States	United States – random breds
Russian Blue	Europe	
Savannah	Species hybrid	Serval × domestic
Scottish Fold	Natural mutation	United Kingdom – random breds, British Shorthair, Persian, Exotic
Selkirk Rex	Natural mutation	United States – random breds, Persian, British Shorthair, Exotic
Siamese	Southeast Asia	Balinese, Havana Brown, Javanese, Colorpoint, Oriental
Siberian	Europe	Russian – random breds
Singapura	Variant	Bombay, Burmese, Tonkinese
Sokoke	Arabian Sea	African – random breds
Somali	Variant	Abyssinian
Sphynx	Natural mutation	Devon Rex
Tonkinese	Variant	Bombay, Burmese, Singapura
Turkish Angora	Mediterranean	
Turkish Van	Mediterranean	

*Modified from genetic studies based on 29 tetranucleotide short tandem repeat markers, 39 dinucleotide short tandem repeat markers,[90–92] and unpublished data (LA Lyons)

By considering breed relationships, genetic health concerns across cat populations and breeds can be inferred due to inheritance via outcrossing.

Table 5 Uncommon mutations for inherited diseases of domestic cats*

Disease	OMIA entry link	Gene	Mutation†
11β-hydroxylase deficiency (congenital adrenal hypoplasia)[95]	001661-9685	*CYP11B1*	Exon 7 G>A
Dihydropyrimidinase deficiency[96]	001776-9685	*DPYS*	c.1303G>A
Factor XII deficiency[97]	000364-9685	*FXII*	c.1321delC
Fibrodysplasia ossificans progressiva	000388-9685	unpublished	unpublished
Gangliosidosis 1[98]	000402-9685	*GLB1*	c.1448G>C
Gangliosidosis 2[99,100]	001462-9685	*HEXB*	c.1467_1491inv c.667C>T
Gangliosidosis 2[74]	001427-9685	*GM2A*	c.390_393GGTC
Hemophilia B[101]	000438-9685	*F9*	c.247G>A c.1014C>T
Hyperoxaluria[102]	000821-9685	*GRHPR*	G>A I4 acceptor site
Hypothyroidism	000536-9685	unpublished	unpublished
Lipoprotein lipase deficiency[103]	001210-9685	*LPL*	c.1234G>A
Mucolipidosis II[104]	001248-9685	*GNPTAB*	c.2655C>T
Mannosidosis, alpha[105]	000625-9685	*LAMAN*	c.1748_1751delCCAG
Mucopolysaccharidosis I[106]	000664-9685	*IDUA*	c.1107_1109delCGA c.1108_1110GAC
Mucopolysaccharidosis VI[94]	000666-9685	*ARSB*	c.1427T>C
Mucopolysaccharidosis VI[93,107]	000666-9685	*ARSB*	c.1558G>A
Mucopolysaccharidosis VII[108]	000667-9685	*GUSB*	c.1052A>G
Muscular dystrophy[68]	001081-9685	*DMD*	900bp del M promoter – exon 1
Niemann–Pick C[109]	000725-9685	*NPC*	c.2864G>C
Polydactyly[17]	000810-9685	*SHH*	c.479A>G c.257G>C c.481A>T
Porphyria (congenital erythropoietic)[110]‡	001175-9685	*UROS*	c.140C>T c.331G>A
Porphyria (acute intermittent)[111]‡	001493-9685	*HMBS*	c.842_844delGAG c.189dupT c.250G>A c.445C>T
Vitamin D resistant rickets[112,113]	000837-9685	*CYP27B1*	c.223G>A c.731delG c.637G>T

*The presented conditions are not prevalent in breeds or populations but may have been established into research colonies. †Not all transcripts for a given gene may have been discovered or well documented in the cat; mutations presented as interpreted from original publication. ‡A variety of mutations have been identified, yet unpublished, for porphyrias in domestic cats. Contact PennGen at the University of Pennsylvania for additional information. OMIA: Online Mendelian Inheritance in Animals (omia.angis.org.au) entries provide links to citations and clinical descriptions of the phenotypes and the diseases. Listed citations are for the causative variant discovery

Persian cat breed family

Figure 6 The Scottish Fold (a) and the Selkirk Rex (b) are derived from random-bred cats that had novel ear and hair coat variants, respectively, and have been molded by crossing with Persians (c) to obtain structure and facial and head morphology. The Selkirk Rex and Scottish Fold are at risk for polycystic kidney disease due to the outcrossing with the Persian (see Figure 5). These cats segregate for longhair variants common to the Persian and have a variety of coloration variants. The Scottish Fold is an orange and white tabby (***A-, B-, C-, D-, E-, I-, Ll, O-, Ss***), the Selkirk is a black smoke (***aa, B-, C-, D-, E-, I-, ll, oo, ss***) and the Persian is cream and high white (***aa, B-, C-, dd, E-, I-, ll, O-, SS***). *Images courtesy of Animal Photography*

If a newly recognized condition is suspected in cats, based on a number of individuals presenting similarly, researchers will generally consider testing for the known variant as a non-commercial service and may continue analysis of the entire gene to determine if new DNA alterations can be identified that are causative for this particular condition. Other biomarkers are also available at these specialized laboratories to help decipher between specific conditions, such as the lysosomal storage diseases and metabolism disorders.

And the 'ugly' cat variants – be careful with selection

Most cat genetic tests developed to date have been for traits that have nearly complete penetrance, little variability in expression and early onset. However, some recognized DNA variants in cats might be considered risk factors, predisposing an individual to a specific health problem. These are not clean and clear, simple genetic traits, but complex risk factors and susceptibilities with 'ugly' genetics. Undoubtedly, the majority of the variation in the genome will prove to be modifiers; that is, polygenes that have DNA variants with small heritable effects. Research has thus far focused on just the tip of the iceberg – deciphering 'ugly' genetic variation is the future.

The reasons why a condition might not present when a specific DNA variant is present have been predicted and are now being deciphered as we understand more and more about the entire genomic sequence. Environmental interactions certainly play a role in the overall appearance and health of an individual and its organs. There are also several known genetic mechanisms and other factors that can make DNA variants more difficult to interpret and their consequences more difficult to predict (see box below).

Some recognized DNA variants in cats are not clean and clear, simple genetic traits, but complex risk factors and susceptibilities with 'ugly' genetics.

HCM variants

An excellent example of a variant that confers a risk is the DNA variant associated with cardiac disease in cats. Hypertrophic cardiomyopathy (HCM) is a recognized genetic condition.[114] In 2005, Drs Meurs, Kittleson and colleagues published findings that a protein alteration, A31P, in the *cardiac myosin-binding protein C 3* (*MYBPC3*) gene was strongly associated with HCM in a research colony of Maine Coon cats at the University of California – Davis.[75] The data clearly showed that not all cats with the variant had HCM and some cats with HCM did not have the DNA variant. Age of onset, variable expression and disease heterogeneity were discussed as confounding factors in this study. This suggested that the identified DNA variant should be considered more of a 'risk factor' than a directly causative variant.

Subsequent studies have shown that not all Maine Coon cats with the A31P variant develop HCM,[115,116] and one of those papers has interpreted this lack of penetrance as being evidence that the A31P variant is not causal.[116] This interpretation is misleading, and has led to debate as to the validity of the Maine Coon HCM test. As is true in humans with cardiac disease, the finding that not all cats with the A31P variant in *MYBPC3* develop HCM is actually usual in the field of HCM genetic testing. The controversy has prompted correspondence within the literature and continued studies to clarify the interpretations.[117] Further, an additional variant in *MYBPC3*, known as A74T, was suggested at a scientific meeting as being causative for HCM. When some commercial testing laboratories started offering the A74T test to the cat community, it became evident that A74T was a polymorphism occurring in a large number of breeds, and was not significantly correlated to HCM; rather, A31P penetrance was incomplete but highly associated with disease.[118]

Factors that can hamper genetic interpretation

- **Incomplete penetrance** For some traits and diseases, even though a known causative variant has been identified, an individual with that variant may not present with the condition in the case of incomplete penetrance.
- **Age of onset (age-related penetrance)** Some diseases have a slow progression and may not develop until later in life. Basically, the cat needs to be monitored for a long period to determine if it is a carrier for an undesired trait, or is clear of the disease.
- **Variable expression** Most traits and diseases have some degree of variable expression, depending on the individual. Some cats with PKD have only a few cysts and never progress to kidney disease; others have severe and rapidly progressive disease and succumb to renal failure early in life.
- **Disease heterogeneity** Often, more than one variant in a single gene, or variants in different related genes, can cause the same disease. Genetic heterogeneity for HCM in humans is a well established example and there is no reason why the same might not be true in cats.
- **Genetic testing accuracy** Even though a specific genetic variant may be identified for a trait or disease, research laboratories use different methods to assay for the variant. Errors in genetic assays may produce inaccurate DNA results, leading to confusion in genetic test interpretation.
- **Inaccurate clinical diagnosis** As in the genetic laboratory, standard procedures and definitions, equipment sensitivity, and training and experience of the veterinarian or veterinary technician all affect the accuracy of diagnoses.

Other disease variants

Like HCM variants, other disease variants in cats have shown variation in penetrance and expression. The *CEP290* PRA variant in Abyssinians has a late age of onset and some cats with subclinical disease have been identified.[119] Some cats with the pyruvate kinase deficiency can have very mild and subclinical presentations.[120] Thus, disease- or trait-causing variants may not be 100% penetrant, and so may not always cause clinically detectable disease.

Blood type variants

Cats are one of the few species to have had the variant for their blood type determined. Blood type incompatibilities 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 indicative of the B blood type or a B blood type carrier.[71] Because both variants are on the same allele, the true causative variant has not been definitively determined. Thus, at the current time, both variants should be examined in cats to genetically determine blood type. Some laboratories have been identified that are not only typing the incorrect variant, but also not both variants. Breeders generally are the first to recognize when a genetic testing laboratory is making errors. Laboratories associated with research groups are most likely to correct errors and perform further studies to improve their testing accuracy.

No genetic tests are validated in hybrid cat breeds, although the tests are typically used very frequently in Bengal cats.

Hybrid cats

Several cat breeds have been formed by crossing domestic cats (*Felis catus*) with different wild species of cat. The Bengal breed is acknowledged worldwide and has become highly popular. To create Bengals, Leopard Cats (*P bengalensis*) were (and continue to be) bred with Egyptian Mau, Abyssinian and other cats to form a breed that is unique in both color and temperament.[67] The Chausie is developing from crosses with Jungle Cats (*Felis chaus*), and Savannahs from crosses with Servals (*Leptailurus serval*). Bobcat (*Lynx rufus*) hybrids have not been genetically proven to date.

The 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.[121] The Jungle Cat is more closely related to a domestic cat than is the Leopard Cat. In addition, for some of these wild felid species, different subspecies have been incorporated into the breed.

Comparison of the DNA sequence between a domestic cat and one of these wild felid species will reveal many (possibly several percentage) genetic differences – fewer for the Jungle Cat, more for the Serval. The genetic differences are most likely silent (neutral) variants, but the variation will interplay with genetic assays and may cause more test failures or inaccuracies than would normally be

Parentage testing, and individual, breed and race identification

Standardized genetic tests are important for sharing information, combining datasets and assisting with population management. Peer-review, research collaborations, forums and comparison tests hosted by the International Society of Animal Genetics (ISAG) allow both formal and informal oversight of parentage test development in domesticated species. Under the auspices of ISAG, a microsatellite-based DNA profiling panel for parentage and identification in the domestic cat has been developed, and vetted by 17 worldwide commercial and research laboratories.[123] Nine microsatellite DNA markers and two additional gender markers are sufficient for parentage, gender determination and identification testing of random-bred and purebred cats and several wild felid species. Although no cat breed registry makes use of this technology to prove the accuracy of pedigrees, the opportunity does exist and is offered by laboratories around the world.

Genetic studies have been able to differentiate eight worldwide populations ('races') of cats.

A newly developed test for the domestic cat is a race and breed identification panel, a Cat Ancestry panel. Based on studies by Lipinski et al[90] and Kurushima et al,[91] microsatellites (aka short tandem repeats [STRs]) and single nucleotide polymorphisms (SNPs) have been tested in a variety of random-bred cats from around the world and in the majority of the major cat breeds of the USA and other regions. The genetic studies have been able to differentiate eight worldwide populations of cats – races – and can distinguish the major breeds.

Many cat breeds should be considered as genetic family groups (Table 4). Phenotypic markers help to delineate breeds within specific breed families, such as the Persian, Burmese and Siamese families. For example, the *Fold* DNA variant of a Scottish Fold will demarcate an individual in the Persian family as being a Scottish Fold and not an Exotic Shorthair. The cat race and breed identification tests are similar to tests that have been developed for the dog. The situation differs, however, in that domestic cats are from random-bred populations that existed in different regions of the world for thousands of years, and not a concoction of pedigreed breed cats. Therefore, most random-bred cats will match to a regional population of cats (a 'race' of cats), and not to a mixture of different breeds. Further, while many feral dogs are actually breed mixes, feral cat populations existed long before the breeds; thus the breeds are subsets of the gene pools of feral cat populations.

anticipated. No genetic tests are validated in the hybrid cat breeds, although the tests are typically used very frequently in Bengal cats. Thus, the accuracy of any genetic test is not known for hybrid cat breeds. Consider, for example, the charcoal coloration in the Bengal cat.[122] This is due to the cats having one allele from the Leopard Cat, A^{Pbe}, for *Agouti* and their second allele from the domestic cat for non-agouti, *a*. If Bengal cats can have alleles from different species for color, there is the possibility of different alleles at all other genes in their genome as well.

Whole-genome sequencing for feline health care

DNA testing for diseases and phenotypic traits of domestic cats is a rapidly growing asset for veterinary medicine. A number of commercial laboratories around the world can now perform cat genetic diagnostics (Table 3), allowing both the veterinary clinician and the private owner to obtain DNA test results. DNA is easily obtained from a cat via a buccal swab using a standard cotton bud or cytological brush, and samples may be sent to any of these laboratories. Test results identify carriers of traits, predict the incidence of traits for breeding programs, and influence medical prognoses and treatments. Besides controlling the occurrence of disease, one long-term goal of identifying these genetic variants is the correction of the defect via gene therapies and designer drug therapies. Thus, genetic testing is an effective preventative medicine tool and a potential ultimate cure through selective breeding. However, genetic diagnostic tests may still be novel for many veterinary practitioners and their application in the clinical setting needs to be subject to the same scrutiny as any other diagnostic procedure.

Genetic testing has been a part of modern human health care in the USA since the implementation of the DNA mutation test for phenylketonuria (PKU) in the 1960s.[124] Most individuals in the USA do not realize that, at birth, after a heal prick blood collection, they were tested for a battery of genetic diseases. Similar testing is now available to the public as an elective evaluation of a person's genome. Companies, such as 23andMe (23andme.com), offer a personal genetics service that presents an individual with their own variants for known single gene traits and also variants that confer risk. Similar offerings are available for domestic cats. Clearly, these genetic services must not replace the role of the clinician or veterinarian, since the interpretation of the genetic results should be made by a professional as part of an overall health care plan. Many laboratories, such as the University of California – Davis (vgl.ucdavis.edu), offer both the majority of the genetic tests important for cat breeds and also a Cat Ancestry panel that can determine a cat's race and potential breed.

What are currently recognised as sporadic or idiopathic conditions will slowly be determined to have individual specific genetic causes, leading to highly specific personalized medicine for our companion animals.

However, in humans, and hopefully cats, too, the future of individual health care will rely on the individual's personal genome. A result of the Human Genome Project has been the development of rapid and cost-effective means to sequence an entire genome of an individual in less than a month. Currently, whole-genome sequencing is becoming the standard of health care for genetic profiling of cancers, with 'cancer genomics' dictating the selection of chemotherapies based on DNA mutations of the tumor.[125] At specialized centers around the world, newborns with sporadic, congenital abnormalities can be whole-genome sequenced, which often, but not always, detects the cause of their maladies.[126] Since over 100,000 people have now had their genomes sequenced, the database of normal and detrimental genetic variants is fairly well defined in some human populations, though requires substantially better definition in others.[127] Likely, whole-genome sequencing will become part of the health care package for human health.[128] Recently, the $1000 genome has been achieved for humans, and shortly this technology will be adapted for other species.[129]

For cats, currently whole-genome sequencing is being used to investigate diseases and traits that are known to be heritable, and also when sufficient individuals are not available for a different means of genetic analysis, such as family studies or case-control association studies. Like humans, eventually the genetic variant databases will be sufficient for the analysis of an individual cat with an unusual health presentation. The 99 Lives Cat Genome Sequencing Initiative (felinegenetics.missouri.edu/ninety-nine-lives) has been launched to meet the same standard in health care for cats as for humans. What are currently recognised as sporadic or idiopathic conditions will slowly be determined to have individual specific genetic causes, leading to highly specific personalized medicine for our companion animals.

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Conflict of interest

The author declares that there is no conflict of interest.

KEY POINTS

- 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 need to be considered.
- Understanding the relationship of cats to the race of origin and their breed families can be predictive for healthcare issues.
- Some traits are highly desired and genetic testing can help breeders to more accurately determine appropriate breedings; thus, potentially becoming more efficient breeders, and lowering costs and helping to address overpopulation.
- Other traits or diseases are undesired. In this context, genetic testing can be used to prevent disease and potentially eradicate the concern from the population.
- Genetic tests for simple genetic traits are more consistent with predicting the trait or disease presentation, but, as genomic research progresses for the cat, tests for variation that confers risk will become more commonplace.
- Veterinarians will have to consider the significance of a risk-conferring disease variant as part of their differentials and treatment plans, and breeders will have to consider these same risk factors, along with the other important attributes of a cat, in their breeding decisions.

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