Review

Recent advances in cat genetics

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Abstract

The domestic cat has indirectly benefited from the human genome sequencing project, which has fostered new technologies and research designs that benefit all domesticated animals and breeds. Consequently, the genome project of the domestic cat has taken a significant leap forward, pouncing into the limelight. A variety of genetic tests for inherited cat diseases and phenotypic traits are now available, making genetic technologies and DNA testing common tools for cat breed husbandry and health management. Cat breeders and veterinarians can now use genetics to more efficiently breed cats, resulting in cats that also have lower risks of health concerns. As in humans, designer medicine, which is predictive, preventative, personalized and participatory, is a growing reality for the cat. The cat's own genome sequencing project is about to mature from its 'kittenhood', which will allow studies of complex diseases feasible in the near future. Common cat diseases, such as asthma, diabetes, hyperthyroidism, urinary tract syndromes and susceptibilities to infectious diseases, including feline infectious peritonitis, have some heritable component, whether found in fancy cat breeds or in the random bred house cat. Genetic resources developed from the cat genome project will assist the genetic evaluation of these traits, traits that are commonplace in the private practice clinicians' patient load. This review presents the current state of cat genetic testing, the current abilities of the feline geneticist, the expected resources, and outcomes of the cat genome sequencing project, and the role of veterinary specialists and private practice clinicians in feline genetics.

Keywords: Domestic cat, *Felis catus*, Feline, Comparative genomics, Inherited disease, Genetics

Review Methodology: I searched the following databases: CAB Abstracts, CAB Heritage, Agricola and Pubmed (Keyword search terms used included coat color, domestic cat, *Felis catus*, feline, inherited disease). In addition, I used the references from the articles obtained by this method to check for additional relevant material. I also spoke to colleagues and checked for any upcoming studies not yet published.

Cat Origins

Domestic felines and humans have a symbiotic, mutual tolerance for one another that developed as humans became civilized. Several independent sites of early civilizations are known, including the Yellow River region of China, the Indus Valley in Pakistan and the Fertile Crescent region which extends from Iraq, into Turkey, south along the Mediterranean coast and into the Nile Valley of Egypt [1]. As humans transitioned from hunter-gatherers to the more sedentary lifestyle of the farmer, permanent settlements subsequently developed. Within these villages, refuse piles and grain stores established, attracting mice and rats, a primary prey species for the small wildcat. To obtain these easy meals, the cat came to tolerate humans, thereby actively participating in their owner domestication.

The ancestor of the domestic cat is likely one or more of the many known subspecies of small wildcats, such as the European wildcat, *Felis silvestris,* and or African wildcat, *Felis libyca* [2]. These wildcats are usually considered separate species and distinct from the domestic cat, however, the wildcats produce fertile hybrids with domestic cats [3]. Thus the true speciation of these small

felids can be debated and introgressions between the true wildcat and domestic cats may be an ongoing process [4–7]. Many other subspecies of European, Asian and African wildcats have been described [8, 9] and their contributions to the domestic cat are unknown. Hence, the true origins and the number of events that led to the domestication of the cat has not been completely resolved, a remaining feline mystery.

Recent genetic studies have shed some light on the domestication of the cat [10, 11]. These studies support Near East wildcat subspecies as the most likely contributors to cat domestication and those domestic cats from the region, particularly Turkey, have the most genetic diversity. However, not all subspecies from this and other Asian regions have been sufficiently considered, thus, contributions from other wildcat subspecies should continue to be evaluated. These investigations strongly support the association of cat domestication with agricultural development in the Near East within the past 10 000 years. Wildcats from South Africa (*Felis silvestris caffra*) appear to have had little or no contribution to the domestic cat. When does the cat begin to seek human affection and companionship and when does man develop the first controlled cat breeding programs? These aspects of the domestication process are not fully resolved.

Cats have been identified as part of human burial sites, suggesting their importance as a companion [12]. Reviews of early artwork and other archaeological evidence from Egyptian excavations clearly support the early taming of the cat in Egypt [13]. Regardless of where or when cat breeding developed, domestication of the cat is one of the most recent for our companion animals [14], distinctive from the much earlier domestication of the worlds other favourite companion animal, the domestic dog [15, 16]. Thus, the dynamics of genetic variation across cat breeds is likely significantly different from species that have more ancient domestication events, longer breed histories and more intense selection processes.

Cat Breeds

Cat breed dynamics are significantly different from other companion and agricultural species. These nuances are important for the development of the appropriate genetic tools, resources and techniques that will be the most beneficial and efficient for cat genetic research and health programs. Random bred and feral cats represent the overwhelming majority of cats throughout the world, not fancy cat breed populations. Early studies on coat colour phenotypic frequencies in cats have suggested their dispersal via commerce and some selective pressures based on novelty selection [17]; however, the wide dispersal of the cat, combined with large population sizes and random mating, suggests little sub-structuring in the worldwide population. Considering the worldwide distribution of cats, the USA has the highest proportion of purebred cats. Nearly 10 000 feline clients visit the University of California – Davis Veterinary Medicine Teaching Hospital per year; however, only 10–15% are represented by purebred cats [18]. Feral cats still play a major role influencing the genetics of our pet cats, but less so for cat breeds [19]. Thus, population studies for complex traits will likely require genetic markers and linkage disequilibrium (LD) estimates in a variety of random bred cat populations, as a majority of health problems will be ascertained from these outbred populations.

The first documented cat shows that judged cats on their aesthetic value occurred in London, England at the Crystal Palace in 1871. This first competition presented only a handful of breeds, including the Persian, Abyssinian and Siamese. Various encyclopaedic volumes pertaining to the domestic cat list approximately 50–80 cat breeds, worldwide [20, 21]. However, a majority of breeds has developed in the past 50 years and many listed breeds did not develop into viable populations, hence lost to posterity. Table 1 lists the most pertinent cat breeds and their genetic relationships. Most worldwide cat fancy associations, such as the Cat Fanciers' Association (CFA) [22, 23], The International Cat Association (TICA) and Feline International Federation (FIFe), recognize approximately 35–41 cat breeds; however, only a few breeds overwhelmingly dominate the breed populations. Persian cats and their related breeds, such as Exotic Shorthair, a shorthaired Persian variety, are the most popular cat breeds worldwide, and represent an overwhelming majority of purebred cats. Although not all cats produced by breeders are registered, perhaps only 20–30%, the CFA, one of the largest cat registries worldwide, generally registers approximately 40 000 total purebreds annually. Approximately 16 000–20 000 are Persians and approximately 3000 are Exotic Shorthairs, implying one group of cats, the Persian group, represents approximately 50% of the cat fancy population [24]. Common breeds that generally have at least 1000 annual registrants are Abyssinians, Maine Coon cats and Siamese. Other popular breeds include Birman and Burmese. Most of these popular breeds also represent the oldest and most established cat breeds worldwide, thus genetic tools and reagents should primarily focus on domestic cats and a handful of other fancy cat breeds.

Additionally, sub-structuring of the breeds may need to be considered for genetic applications [11, 25]. Many breeds derive from an older breed, thereby forming breed families or groups (Table 1, Figure 1). Approximately 19 breeds can be considered 'foundation' or 'natural' breeds, implying that many other breeds have been derived from these foundation cats. Derived breeds are often single gene variants, such as longhaired and shorthaired varieties, or even a no haired variety, as found in the Devon Rex and Sphynx grouping. Colour variants also tend to demarcate breeds, such as the 'pointed' variety of the Persian, known as the Himalayan by many cat enthusiasts and even as a separate breed by some associations,

Table 1 Genetic definition of major cat breed families

	Breed	Date/place founded	Breed (family) grouping[1]
1	Abyssinian	Founder – India?	Somali
2	American Curl	Mutation	USA – random bred
3	American Shorthair	Founder – USA	American Wirehair
4	American Wirehair	Mutation	American Shorthair
5	Balinese	Variant	Colorpoint, Havana Brown, Javanese, Oriental, Siamese
6	Bengal	Hybrid	Leopard cat×Egyptian Mau and Abyssinian
7	Birman	Founder – Southeast Asia	
8	Bombay	Variant	Burmese, Singapura, Tonkinese
9	British Shorthair	Founder – Europe	Scottish Fold
10	Burmese	Founder – Southeast Asia	Bombay, Singapura, Tonkinese
11	Chartreux	Founder – Europe	
12	Colorpoint Shorthair	Variant	Balinese, Havana Brown, Javanese, Oriental, Siamese
13	Cornish Rex	Mutation	UK – random bred
14	Devon Rex	Mutation	UK – random bred, Sphynx
15	Egyptian Mau	Founder – Mediterranean	
16	Exotic	Variant	Persian
17	Havana Brown	Variant	Balinese, Colorpoint, Javanese, Oriental, Siamese
18	Japanese Bobtail	Founder	
19	Javanese	Variant	Balinese, Colorpoint, Havana Brown, Oriental, Siamese
20	Korat	Founder – Southeast Asia	
21	Maine Coon	Founder – USA	
22	Manx	Mutation	UK – random bred
23	Norwegian Forest	Founder – Europe	
24	Ocicat	Crossbred	Siamese×Abyssinian
25	Oriental	Variant	Balinese, Colorpoint, Havana Brown, Javanese, Siamese
26	Persian	Founder – Europe	Exotic
27	Ragdoll	Founder – USA	USA – random bred
28	Russian Blue	Founder – Europe	
29	Scottish Fold	Mutation	UK – random bred, British SH, Persian
30	Selkirk Rex	Mutation	USA – random bred
31	Siamese	Founder – Southeast Asia	Balinese, Havana Brown, Javanese, Colorpoint, Oriental
32	Siberian	Founder – Europe	Russian – random bred
33	Singapura	Variant	Bombay, Burmese, Tonkinese
34	Sokoke	Founder – Africa	African – random bred
35	Somali	Variant	Abyssinian
36	Sphynx	Mutation	Devon Rex
37	Tonkinese	Variant	Bombay, Burmese, Singapura
38	Turkish Angora	Founder – Mediterranean	Turkish Van
39	Turkish Van	Founder – Mediterranean	Turkish Angora

[1]Modified from genetic studies of Menotti-Raymond *et al.* [25, 88], which is based on 29 tetranucleotide STRs, and Lipinski *et al.* [11], which is based on 39 dinucleotide STRs. A mutation breed implies a newly identified genetic trait within cats, a variant breed implies an established mutation that has been added to a foundation breed to produce a new breed that has one genetic variant different from the foundation breed.

such as TICA [26]. Many cat breeds originated from single gene traits, such as folded ears of the Scottish Fold [27] and dorsally curled pinnea of the American Curl [28], and then later developed into a more unique breed based on conformation. Recognition of newly identified spontaneous mutations, novelty selection, often occurs in cats from random bred populations, followed by morphological moulding with various desired breed combinations in order to construct a new breed. Thus, many new and some established breeds have allowable outcrosses to random bred cats and specific breeds to influence the 'type' and to support genetic diversity in the new breed's foundation. Persians have a highly desired brachycephalic head type, thus they tend to influence many breeds. Breeds desiring the dolichocephalic type often outcross with the Siamese family of cats. The outcrosses that are valid for any breed can vary between cat registries and the same breed may have a different name depending on the country. For example, the Burmese registered by the Governing Council of the Cat Fancy (GCCF) in the United

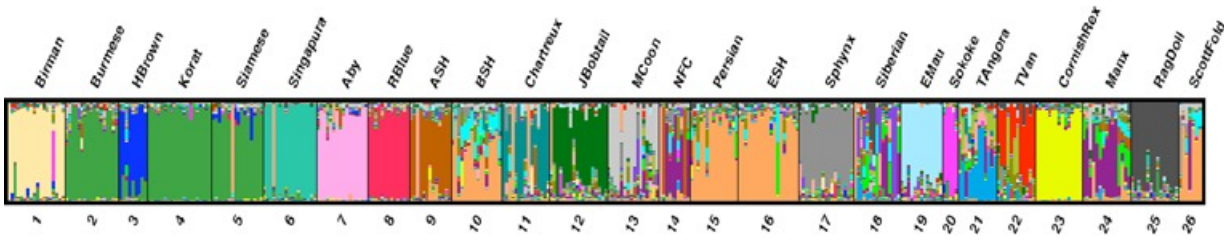

Figure 1 Structure analysis of 26 cat breeds with 38 STRs. The analysis includes unrelated cats selected from USA populations of each breed. Most cats representing different breeds group into specific breed populations, which are represented by the 19 different colours of the figure. Each bar represents an individual cat, the colour of the bar represents the most likely genetic signature constituting each individual. Persians, Exotics and Scottish Folds all have the same colour, thus, cannot be demarcated as separate breeds when all cats are analysed together. British Shorthairs also show a strong association with the Persian group. The Southeast Asian breeds, Siamese, Korats and Burmese also group strongly. The Siberian breed has a variety of genetic contributions, suggesting it is less sub-structure into a breed, consistent with its recent development. Individual cats with a different colour within a breed group have been proven to be misidentified or recent importations from random bred populations. The Turkish Angora (TAngora) and Turkish Van (TVan) groupings also show high variation and represent a mixture of USA cats and cats imported from Turkey. Abbreviations: Havana Brown (HBrown), Abyssinian (Aby), Russian Blue (RBlue), American Shorthair (ASH), British Shorthair (BSH), Japanese Bobtail (JBobtail), Maine Coon (MCoon), Norwegian Forest Cat (NFC), Exotic Shorthair (ESH), Egyptian Mau (EMau) and Scottish Fold (ScottFold)

Kingdom and the FIFe in Europe are known as the Foreign Burmese breed in the USA and these cat 'breeds' have significantly different craniofacial type between the countries. Some breeds, such as Korats and Turkish Vans, have very similar standards across most all countries and registries, although outcrossing and importation rules many still vary. Interestingly, some cat breeds are actually hybrids between clearly different species of cats and the domestic cat. Asian leopard cats (*Felis* (*Prionailurus*) *bengalensis*) are part of the foundation of the Bengal breed [29], which is a highly popular breed worldwide, but not registered by the CFA. Serval hybrids (*Felis serval*), known as Savannahs, and Jungle cat hybrids (*Felis chaus*), known as Chaussies, are also growing in popularity. Hence, genomic tools should give some attention to these three cat species to support disease studies within these hybrid cat breeds.

From a phylogenetic point of view, cat breeders are 'splitters' instead of 'lumpers' and a few foundation breeds encompass most of the variation found in cat breeds. An evaluation of 38 microsatellite markers in 19 cat breeds, 12 random bred populations and 3 wildcat subspecies has revealed some of the basal relationships of the foundation cat breeds as depicted by the phylogenetic tree in Figure 2 [11]. The relationships show that breeds that are documented derivatives strongly cluster, such as the Singapura and the Burmese or the Havana Brown and the Siamese. Newly developing breeds from eastern Africa, such as the Sokoke, adhere to their feral relatives, cats from the Kenyan islands of Lamu and Pate. Additionally, three 'clusterings' of cats appear to be evident: cats from the Far East, such as the Siamese, Burmese, Havana Brown, Singapura, Korats and Birmans; cats with Arabic influence, such as the wildcats and Kenyan cats; and cats from the Mediterranean, which includes most of all other breeds and populations. The genetic data of the cat breeds and various different 'genetic clustering algorithms, such as the software Structure [30] can be used to assign cats to specific breeds. Considering the 19 foundation populations of cat breeds, the cat genetic data can correctly assign an unknown individual to their respective breed with 98% accuracy (Figure 1). This same technique is the scientific foundation to the different breed identification tests that are commercially available for the dog, such as the Canine Wisdom Panel (Mars, Inc.) or the Canine Heritage Panel (MMI Genomics).

Because the cat genetic studies have included regional random bred populations, cat breeds can also be assigned to their world region of origin. For example, some Far Eastern cat breeds, such as Birman and Burmese, are clearly defined, while others, such as Singapura and Burmese cannot be defined from one other. Regardless of the genetic resolution between the individual breeds, all Far Eastern breeds are more closely related to their feral cousins than breeds from the west or western feral cats. Abyssinians appear to be a strongly demarcated breed, while the more European breeds are slightly less genetically distinct from one another. In recent years, random bred or feral populations of cats have developed into newer, regional specific breeds, such as the Siberian from Russia and the Sokoke from Africa. These two breeds have high genetic variation, implying high heterozygosity, comparable with random bred populations [11].

Cat Phenotypic Variation

Single gene mutations established many of the cat breeds and many breed populations' segregate for the variant and normal alleles. Approximately 30 single gene phenotypic variants are identified in domestic cats and associated breeds, including dominant, co-dominant, recessive,

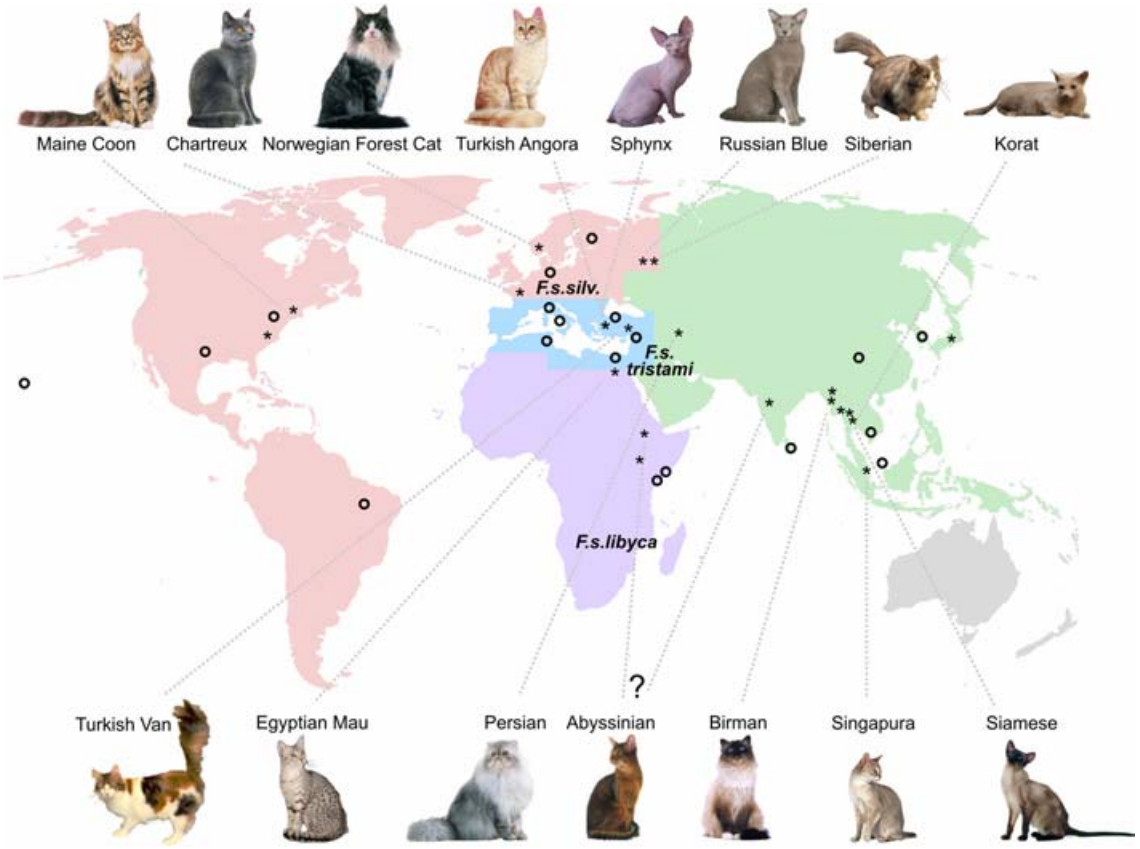

Figure 2 Cats breeds and their populations of origin. Analysis from Lipinski *et al*. [11] showing the location of cat breeds and their association with random bred populations. Stars represent cat breeds, circles represent random bred populations, and wildcats are listed as their genus species, *Felis silvestris silvestris* (*F. s. silv.*), *Felis silvestris tristami* and *Felis silvestris libyca* (*caffra*)

sex-linked and homozygote lethal traits (Table 2). Genetic heterogeneity and the pleiotropic and epistatic effects of cat coat colorations allow cats to be an excellent primer for basic and advanced genetic instruction. Although one of the first traits to be mapped to a particular chromosome in any species was the sex-linked orange coloration of the cat [31, 32], genetic studies have localized the trait, but the gene and mutation remains elusive [33, 34]. The first autosomal trait linkage in the cat was recognized 70 years later between the polymorphisms for haemoglobin and the Siamese pattern caused by mutations in *tyrosinase* [35]. Now that genomic tools for the cat have become effective, the genetic mechanisms for many cat phenotypes are being deciphered, including the Siamese pattern, which is called 'points' [36, 37]. The pointed coloration found in Siamese and Himalayans was easily identified because the causative gene, *tyrosinase*, produces similar phenotypes in other species, such as the Himalayan rabbit [38]. To date, most phenotypic mutations in the cat have been identified by a candidate gene approach because an obvious enzymatic mechanism has been disrupted or the same coat coloration has been documented by other species (Table 3). Family-based linkage studies also have implicated candidate genes, such as *KIT* and white spotting [39], but other linkage analyses have implicated genetic regions with no known candidates, such as chromosome B1 and the *Tabby* locus [40]. To date, all the coloration mutations in cats have been shown to be the same in different breeds and are likely identical by descent. However, long fur has been shown to have at least four potentially causative mutations in cats, hence not one mutation identical by descent and different breeds having more than one of the identified mutations [41, 42].

Cat Disease Mutations

Although many of the phenotypic traits of the cat seem to have mutations that are identical by descent across the breeds, disease mutations are proving to be more distinct across breeds. Documented in the cat are at least 277 disorders or 'phenes' with a heritable component in other species and at least 46 are suggested as single gene traits in cats (http://omia.angis.org.au/). A majority of the 'phenes' is documented in random bred 'pet' cat populations and many have been noted as only one or a few cases. Twenty-two different genes account for the 31 known mutations causing diseases in cats (Table 3).

Table 2 Phenotypic traits of the domestic cat

Locus	Symbol[1]/gene	Phenotypic effect	Type/breed	Inheritance
Agouti	*A, ASIP*	Pigment switch	All cats	AR, A>a
Amber	ns, *MC1R*	Lighter, reddish pigmentations	Norwegian Forest Cat	AR
Brown	*B, TYRP1*	Lighter, brownish pigmentations	All cats	$B>b^2>b$
Colour[2]	*C, TYR*	Temperature-sensitive coloration, albinism	All cats	$C>c^b\geq c^s>c^a$
Dilute	*D, MLPH*	Pigment density	All cats	AR, D>d
Fold[3]	*Fd*[1]	Pinna ventral fold	Scottish Fold	AD, F>f
Gloves	*G, KIT*	White feet	Birman	AR, G>g
Hairless		No or minimal hair	Peterbald	Not documented
	Hr		Sphynx	AR, variable expression
			Kahona	Hr>hr
Inhibitor	*I*[1]	No pheomelanin	All cats	AD, I>i
Kurl	*Cu*[1]	Pinna dorsally curled	American Curl	AD
Long hair	*L, FGF5*	Hair length	All cats	AR, L>l
Manx[3]	*M*[1]	Taillessness	Manx	AD, M>m
Orange	*O*[1]	Orangish hue to all pigmentation	All cats	X-linked, O, o
Polydactyly	*Pd*[1], *SHH*	Extra digits	British	
American	AD, Pd>pd			
Rex	*R, r*	Curled hairs, some absent, Te associated with fur shine	Cornish	AR
	Re, re		Devon	AR
	ns		LaPerm	AD
	Se[1]		Selkirk	AD
	ns		T-Rex	AR
Spotting	*S*[1]	Ventral white	All cats	Co-dominant, additive $S\geq s$
Tabby[4]	*T*	Pigmentation pattern	All cats	$T^a>T^M>t^b$
White	*W*[1]	All white	All cats	AD, W>w
Glitter	ns	Golden shine to fur	Bengal	Not documented
Ojos Azules	ns	Micrognathia and white spotting	Ojos Azules	Not documented
Bobtail	ns	Short tail, some curled	Japanese	All not documented
			Kurilean	
			PixieBob	
Wirehair	*Wh*	Wiry hair	American wirehair	Incomplete dominance, variable expression, Wh≥wh
Merle	ns	White patching	Several breeds	Not documented

[1]Denotes non-wild-type allele. ns implies no locus symbol has been designated.
[2]The Burmese and Singapura are c^bc^b, Siamese c^sc^s, Tonkinese, c^bc^s but these mutations can be found in feral cats of Asia.
[3]The tailless allele is homozygote lethal, folded ear cats have joint and bone defects in the homozygous state.
[4]Tabby patterns have historically been considered to be allelic; however, modifiers appear to affect the pattern versus the locus associated with the presence or absence of a pattern.

However, only twelve disease-causing mutations are segregating in cat breeds. Several of the disease mutations found in cats have been identified in a breed; however, not all are of a concern to the breed as the disease has been eliminated, was a sporadic mutation or is maintained in a research colony.

Most of the earliest disease mutations identified in the cat also have benefited from the candidate gene approach, as similar traits are in other species with known genes and mutations. The first disease mutations found in the cat were identified for a type of muscular dystrophy and a lysosomal storage disease, both of which cause similar and common diseases in humans. The identified promoter mutation in *dystrophin* [43], causes Duchenne Muscular Dystrophy (DMD) in humans, and the identified mutation in *beta-hexosaminidase A* (*HEXB*), causes the well-known lysosomal storage disease (LSD), Sandhoff's disease [44]. Neither condition is prevalent in breeds and do not constitute a breed predisposition. Several other inborn errors of metabolism or LSD were identified in Persians and Siamese (Table 3), but these mutations are maintained only in research colonies of cats with hopes of the development of gene and enzyme replacement therapies [45, 46]. Korats and Persians have more than one metabolism defect and the MPS VI group of cats were found to be compound heterozygotes for mutations in *ARSB* [47]. Korats are a small population breed and this breed continues to segregate for two gangliosidoses, GM1 and GM2, and the pointed phenotype, all of which are undesired traits in the breed.

Two of the most prevalent disorder mutations in the cat cause cardiac and renal disease. Hypertrophic cardiomyopathy (HCM) is a heterogeneous cardiac disease that has been recognized in several breeds, including American Shorthair, Bengals, Ragdolls and Sphynx; however, HCM is scientifically documented as heritable in only the Maine

Table 3 Cat traits and diseases with known mutations

Disease/coat colour	Gene	Mutation	Breeds	References
Agouti[1]	*ASIP*	del122–123	All breeds	4
Amber	*MC1R*	G250A	Norwegian Forest	33
Brown[1]	*TYRP1*	b=C8G b^l=C298T	All breeds	15
Dilution[1]	*MLPH*	T83del	All breeds	13
Colour[1]	*TYR*	c^b=G715T c^s=G940A c=C975del	All breeds	12, 16
AB blood type (type B)[1]	*CMAH*	18indel-53	All breeds	2
Gangliosidosis 1[1]	*GLB1*	G1457C	Korat, Siamese	3
Gangliosidosis 2[1]	*HEXB*	15 bp del (intron)	Burmese	34
Gangliosidosis 2	*HEXB*	inv1467–1491	DSH	18
Gangliosidosis 2	*HEXB*	C667T	DSH (Japan)	14
Gangliosidosis 2[1]	*HEXB*	C39del	Korat	21
Gangliosidosis 2	*GM2A*	del390–393	DSH	19
Glycogen storage disease IV[1]	*GBE1*	230 bp ins 5′–6 kb del	Norwegian Forest	26
Haemophilia B	*F9*	G247A	DSH	9
Haemophilia B	*F9*	C1014T	DSH	9
Hyperoxaluria	*GRHPR*	In press	DSH	31
Hypertrophic cardiomyopathy (HCM)[1]	*MYBPC*	G93C	Maine Coon	20
HCM[1]	*MYBPC*	C2460T	Ragdoll	29
Lipoprotein lipase deficiency[1]	*LPL*	G1234A	DSH	8
Long fur[1]	*FGF5*	C194A, T182A	Most breeds	27
Mannosidosis, alpha	*LAMAN*	del1748–1751	Persian	1
Mucolipidosis II	*GNPTA*	C2655T	DSH	7
Mucopolysaccharidosis I[1]	*IDUA*	del1047–1049	DSH	11
Mucopolysaccharidosis VI	*ARSB*	T1427C	Siamese	24
Mucopolysaccharidosis VI	*ARSB*	G1558A	Siamese	25
Mucopolysaccharidosis VII[1]	*GUSB*	A1052G	DSH	5
Muscular dystrophy	*DMD*	900 bp del M promoter – exon 1	DSH	23
Niemann-Pick C	*NPC*	G2864C	Persian	22
Progressive retinal atrophy[1]	*PRA*	IVS50 + 9T>G	Abyssinian	28
Polycystic kidney disease (PKD)[1]	*PKD1*	C10063A	Persian	17
Polydactyly	*SHH*	A479G	Maine Coon	30
Polydactyly	*SHH*	A479G	PixieBob	UP
Polydactyly	*SHH*	G257C, A481T	DSH	30
Porphyria	*HMBS*	c.842_844delGAG	Siamese	32
Porphyria	*HMBS*	c.189dupT	Siamese	32
Pyruvate kinase deficiency[1]	*PKLR*	13 bp del in exon 6	Abyssinian	UP
Spinal muscular atrophy[1]	*LIX1-LNPEP*	140 kb del, exons 4–6	Maine Coon	6
Sweet receptor	*TAS1R2*	G8224A	Cat Specific	35, 36
Vitamin D resistant rickets	*CYP27B1*	F44I, K42E	DSH	37

UP are mutations that are unpublished to date.
[1]Mutations with commercial or private genetic testing in the cat.

Source:

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Coon cat [48]. A mutation in *myosin C binding protein* (*MYCBP*) is highly correlated with clinical presentation of HCM in the Maine Coon cat [49] and is currently considered the causative mutation, although some debate has arisen in the feline cardiology community. The frequency of HCM has not been clearly established for the Maine Coon breed, but combined with echocardiogram evaluations, an active genetic typing program is assisting the reduction of this disease within the Maine Coon breed. The same mutation has been evaluated in other breeds with HCM, but as in humans, HCM appears to be heterogenic in cats and the mutation is not correlated with disease in other breeds (K. Meurs, personal communication; L. Lyons, data not shown). A mutation in the

Table 3 Footnotes (*Continued*)

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same gene has been identified in Ragdolls and is correlated with HCM [50], supporting that HCM has genetic heterogeneity in the cat.

Other diseases found in the cat, such as polycystic kidney disease (PKD) in Persian cats, have benefited from a combined genetic linkage analysis and candidate gene approach [51, 52]. Feline PKD was first clinically described as an autosomal dominant inherited trait in the 1990s [53, 54]. Approximately 38% of Persians have PKD, worldwide [55–59], making PKD the most common inherited disease in the domestic cat. Over 95% of cats with PKD will develop renal cysts by 8 months of age. Ultrasound has a high accuracy for PKD detect but not perfect concordance with genetic tests [60], which appears to be more accurate when the test is performed properly. Depending on disease severity, cats can live a normal lifespan, 10–14 years, with PKD, or succumb within a few years of onset, similar disease variation and progressions are also seen in humans. Ultrasonographic identification of renal cysts should be combined with genetic testing to determine the rate of progression in PKD positive cats. Like HCM, not all polycystic kidneys are caused by PKD. Studies have shown that other cystic renal diseases may be occurring in the cat as well [61].

Most cat diseases and their mutations are specific to particular breeds; however, any disease found in the Persian or the Siamese families can spread to other breeds due to the influence of these foundation breeds on modifying morphological structures of new and developing breeds. For example, PKD, which affects approximately 38% of Persians worldwide, has also been documented in Scottish Folds, Selkirk Rexes and British Shorthairs, all brachycephalic breeds that have used Persians to modify structure [62]. HCM is considered highly prevalent in Maine Coons, which is a large population breed, but GM1 and GM2 are at low frequencies in a very small population breed, the Korat. Thus, breeders are now enthusiastically using DNA testing to identify carriers, but wrestling with the disease management decisions for their breed.

Thirty mutations cause diseases in the cat, six coat colour and length loci represent an additional 12 mutations, and a blood group mutation is associated with the Type B blood group in cats. Cats have even been shown to lack a 'sweet tooth' due to the pseudogenization of *Tas1r2* sweet receptor gene [63, 64]. Veterinary medicine has identified over 277 traits that could be heritable conditions in the cat and many have been well documented. The identification of several additional mutations should be on the horizon as active linkage studies have implicated genes or genetic regions for white spotting, tabby, orange, progressive retinal atrophy in the Persian and the Bengal, and a craniofacial defect in the Burmese. Improved genetic resources of the Feline Genome Project will expedite mutation discoveries for the single gene traits of the cat and allow cats to be of assistance for complex traits and health conditions.

Feline Genomics

Early chromosome banding studies of the domestic cat revealed an easily distinguishable karyotype consisting of 18-autosomal and the XY sex chromosome pair, resulting in a 2*N* complement of 38 cat chromosomes [65–68]. The traditional groupings of chromosomes into alphabetic groups based on size and centromeric position has only relatively recently been renamed to straight numerical nomenclature for the cat [69]. Basic light microscopy and giemsa banding also showed that domestic cats have a chromosomal architecture that is highly representative for all felids and ancestral for most carnivores [70, 71]. Cats also have easily distinguishable chromosomes, clearly defined by size, position of the centromere, few small acrocentrics and banding patterns. R-, RBG-banding and fragile sites have also distinguished the cat chromosomes [72–75]. Only minor chromosomal rearrangements are noted among the 36 extant felids, most noticeably, a Robertsonian fusion in the South American ocelot linage leads to a reduce complement, 2*N*=36 [65]. The variation of chromosomal sizes allowed for the easy development of chromosome paints for cat chromosomes by flow sorting [76]. Chromosome painting techniques supported the early somatic cell hybrid maps of the cat [77, 78], showing high conservation of chromosomal arrangement to humans [76, 79], specifically as compared with mice [80]. Hence, chromosome painting gave an excellent overview of cat genome organization [81], which greatly facilitates candidate gene approaches since the location of particular genes can be anticipated in cats from comparison with the genetic map of humans [82].

Genetic and radiation hybrid maps of the cat augment the low-resolution genetic comparisons provided by chromosomal studies. The Bengal, a hybrid between domestic cats, primarily Abyssinians and Egyptian or Indian Maus, and different subspecies of Asian leopard cat (*Felis* (*Prionailurus*) *bengalensis*), has been in production since the late 1960s [29]. It is currently a very popular breed with unique coloration and coat patterns, although not all registries will recognize these cats [26]. The evolutionary distance between the parental type cats of the Bengal breed is significant [83, 84], thus, a Bengal pedigree was the basis of the first recombination map for the cat [85]. The Bengal breed has various health concerns and predispositions, such as HCM, retinal degeneration and chronic inflammatory bowel disease. These conditions may be excellent candidates for LD and admixture mapping in the hybrid cat populations. The interspecies hybrid-based linkage map contains approximately 250 microsatellite markers (aka short tandem repeats, STRs) [85] that are effective for the initiation of linkage studies in families segregating for phenotypic traits. Although rudimentary, this map has already assisted targeted candidate gene approaches, as seen for *PKD* [52], linkage analyses for *Tabby* [40], *white spotting* [39] and *Orange* [33]. The genetic map has led to the first disease gene isolated by

positional cloning, *LIX1*, which causes spinal muscular atrophy in the Norwegian Forest cat [86, 87]. An autosomal genetic linkage map based on a large (N=256) multi-generational intra-species cat family, which was maintained by the Nestlé Purina PetCare Company, contains 483 STRs [88]. This meiosis-based map suggests a usually long length of the cat recombination map of 4370 cM, which is longer than most mammalian species.

The 5000_{Rad} radiation hybrid map of the cat has had several re-iterations and currently has a 1.5-MB-resolution, consisting of 1793 markers that support the conserved genomic organization between cats and humans [89–94]. The RH map has also proven useful for assisting with sequence contig construction for the feline genome project.

The cat's importance in human health, comparative genomics and evolutionary studies supported the National Institutes of Health – National Human Genomics Research Institute (NIH-NHGRI) decisions to produce of a low coverage, 2×, sequence of the cat genome (http://www.genome.gov/Pages/Research/Sequencing/SeqProposals/CatSEQ.pdf). Led by the Broad Institute and AgenCourt, approximately 327 037 single nucleotide polymorphisms (SNPs) have been identified in the sequence from the solitary, highly inbred Abyssinian cat [95]. Although light coverage, approximately 65% of euchromatin sequence, the sequence assembly suggests the identification of 20 285 feline gene orthologues. This sequencing effort re-iterated the conservation between human and cat chromosomal organization by identifying 133 499 regions of conservation and identified additional Numt DNA, RD114 and FeLV introgression sites. An extensive LD study was not performed in the random bred and cat breeds; however, the data from the initial analyses suggest that homozygosity deteriorates 3× faster than in the dog, thus, cat association studies will likely require more SNPs than for the domestic dog. An additional 7× coverage of the same cat has been scheduled for completion (http://www.genome.gov/19517271), which will provide a deeper coverage draft sequence of the cat, as well as SNP identification via re-sequencing in prominent breeds. Hill's Pet Nutrition, Inc. supported a private sequencing effort of the cat, which included Sanger-based sequencing of single cats from six different cats, including a random bred and an African wildcat. A majority of these data are to be made available to the public and Hill's has also provided funding to support feline genome resource development, such as a cat SNP array (Hill's Press Release, Topeka, Kansas (20 July 2008)). These combined efforts should lead to the rapid development of an SNP array that will be useful for the study of complex traits in the cat. More thorough LD studies are under evaluation for the domestic cat and its breeds, to assist with the proper development of the cat SNP chip. Knowing the breed dynamics of the species, the first estimates of LD may likely hold true for some breeds but not others and LD will not be as extensive as for particularly dog breeds, but more extensive than that found in humans.

Other supportive evidences of the high diversity of cats stems from STR studies. An internationally tested, microsatellite-based DNA profiling panel developed for parentage and individual identification in domestic cats requires fewer markers than in other species, most cat breeds having adequate variation at all markers [96]. Nineteen microsatellite markers were included in the panel development and genotyped in a variety of domestic cats. Most STR markers consisted of dinucleotide repeats. In addition to the autosomal markers, the panel included two gender-specific markers, *amelogenin*, and *zinc-finger XY*, which produce genotypes for both the X and Y chromosomes [97]. The international cat DNA profiling panel has a power of exclusion comparable with panels used in other species, ranging from 90.08 to 99.79% across breeds and from 99.47 to 99.87% in random bred cat populations; however, only 10 markers were required to obtain adequate exclusion probabilities. Dog breeds and other species generally require 15 or more markers for adequate exclusions across all breeds. The cat international parentage panel includes markers from the first 10 STRs developed in the cat [98], which were used in one of the first murder cases in Canada to use animal-based DNA evidence [99]. These same STRs have been used by various groups studying other felid populations [5, 6, 100].

STR panels have also been developed using tetra-nucleotide repeats for forensic analyses [98, 101]. Along with STRs, mtDNA is also proven useful for forensic applications in cats [102, 103]; however, feline mtDNA analyses are complicated by the transposition of a larger fragment of the mtDNA genome into the nuclear genome [104]. Approximately 7.9 kb of the 17 kb cat mtDNA has subsequently become amplified 38–76 times, forming a tandem repeat macrosatellite with multiple-length alleles segregating in cats populations, including four modern felid species. The analysis of sequence divergence between the Numt genes and the cytoplasmic mtDNA homologues allowed an estimate for the origins of Numt to be 1.8–2.0 million years ago. Numt genes do not function in cats; rather, the locus combines properties of nuclear minisatellites and pseudogenes [105]. Two distinct repetitive motifs at opposite ends of the control region contribute to the relatively large size (1559 bp) of the cat mtDNA. The high mutation rate of this region has been used to help define other South American wild felid populations [106]; however, due to its high rate of heteroplasmy, forensics studies have shied from this area.

Reproductive Technologies

Even with limited genetic resources, the domestic cat has become the focus of research technologies that use reproductive methods to manipulate the cat genome.

Although gene knockouts for cat allergens were proposed, the currently available 'hypoallergenic' cats have been developed by natural breeding methods (http://www.lifestylepets.com/). The scientific support for these hypoallergenic cats is currently unpublished. However, cloning of the cat by either nuclear or chromatin transfer has been successful and even commercialized [107, 108]. At least one company used client provided materials to clone a pet as a commercial adventure; however, this commercial endeavour has been terminated. Clients are now asking veterinarians to collect viable cells from their cats and send them to cloning companies for the eventual use as the sample to clone the donor cat. Besides several domestic cats, two exotic felids, the African wildcat and the Sand Cat, have also been successfully cloned [109, 110]. The cat cloning has exemplified important aspects regarding this highly controversial topic. The first cloned cat, Cc, was cloned from a calico cat, which is a female cat (Rainbow). Rainbow has white spotting and different alleles affecting coat colour (normal versus orange-hue) at the *Orange* locus on the X chromosome. During X-inactivation only the colour allele on the expressed X is active, thus, producing patches of black (normal) or orange coloration. The cloned cat, Cc, did not express the orange allelic variants; hence, apparently X-inactivation did not get reprogrammed during the cloning process [107]. This outcome highlights two important concepts: (1) researchers still do not recognize or understand all the normal biological processes during embryo development and (2) cloned animals can definitely look different from the original, donor individual. The successful cloning of the African wildcat potentially opens avenues for the reintroduction of the genetics of individuals that have been lost to conservation breeding programmes, such as animals that have been sterilized or are too old or unhealthy to breed. However, domestic cat eggs were used for the cloning of the wildcats, hence, their mtDNA is not representative of the endangered species. But overall, cloning may provide unexpected opportunities in conservation, or perhaps in the replication of individuals with certain phenotypes of interest in research. Representing the ultimate of an inbred species, a series of clones from the same individual could foster interesting studies of nature versus nurture. The recent successes with the development of red and green fluorescent protein transgenic cats [111] also support felines as models for novel diseases that are not currently recognized in the cat populations at large, improve the cats role in biomedical research.

Conclusions/Summary

In our households, the cat has only recently been tamed to sit on our laps and developed into different breeds for our aesthetic pleasures. The genetics of the cat is both simple and complex. Coat colours and morphological traits of cat breeds are easily recognized by the lay public and are an excellent means for a simple educational primer in basic genetics. Feline coat colours explain Mendelian modes of inheritance, X-inactivation, pleiotropic effects, variable expression and genetic heterogeneity. In biomedical research, historically the cat has been a less developed model overall, but important for some scientific endeavours, particularly for neurological studies. But now the cat leads the way for companion animals in cloning and transgenic studies due to the advanced knowledge of feline reproductive techniques. Although much biomedical research is focused on human health improvements, feline medicine and health care is also advancing due to the identification of genetic causes for disease, and understanding individual responses to drug therapies and health care management. The complete and in depth sequence of the domestic cat is a resource that promises cat the development of a cat DNA SNP array, leading to the analysis of more complex traits, especially in the realm of infectious diseases that are common to the household pet and feral cats of the world. The advances in feline genetics are showing a rapid transition to applied health care for cats, improving the quantity and quality of life for one of our favourite companions and thereby for ourselves.

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