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Genetic testing in domestic cats

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ABSTRACT

Varieties of genetic tests are currently available for the domestic cat that support veterinary health care, breed management, species identification, and forensic investigations. Approximately thirty-five genes contain over fifty mutations that cause feline health problems or alterations in the cat's appearance. Specific genes, such as sweet and drug receptors, have been knocked-out of Felidae during evolution and can be used along with mtDNA markers for species identification. Both STR and SNP panels differentiate cat race, breed, and individual identity, as well as gender-specific markers to determine sex of an individual. Cat genetic tests are common offerings for commercial laboratories, allowing both the veterinary clinician and the private owner to obtain DNA test results. This article will review the genetic tests for the domestic cat, and their various applications in different fields of science. Highlighted are genetic tests specific to the individual cat, which are a part of the cat's genome.

1. Introduction

Genetic testing has been available in the domestic cat since the 1960's, but as like other species, over the past 50 years, the level of resolution has improved from the chromosome level to the sequence level. Knowing the direct causative mutation for a trait or disease assist cat breeders with the breeding programs and can help clinicians determine heritable presentations versus idiopathic versions of a health concern. Genetic tests cover all the various forms of DNA variants, including chromosomal abnormalities, mtDNA variation, gene loss, translocations, large inversions, small insertions and deletions and the simple nucleotide substitutions. Higher throughput technologies have made genetic testing cheaper, simpler and faster, thereby making cat genetic testing affordable to the lay public and small animal practice clinicians. The genetic resources for cats and other animal species have also opened the doors for animal evidence to be supportive in criminal investigations. This review will highlight the various tests available for the domestic cat and their specific capabilities and role's in cat health and management.

2. Domestic cat genetic testing

2.1. Cytogenetic testing

Some of the earliest genetic testing for any species was the examination of the chromosomes to determine the presence of the normal and complete genomic complement. Early studies of mitotic chromosomes of the domestic cat revealed an easily distinguishable karyotype consisting of 18 autosomal chromosomes and the XY sex chromosome pair, resulting in a 2N complement of 38 chromosomes for the cat genome [1]. 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. Various cytogenetic techniques, such as R-, RBG-banding and fragile site studies, have also helped distinguish and characterize the cat chromosomes [2–5]. Although a sequential numbering of the chromosomes has been suggested [6], the historical classification of chromosomes into morphologic groups has been retained in the cat. Hence 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 midsize and subtelomeric, similar to chromosome B4.

Although the cat genome is conserved to humans, certain well-known chromosomal abnormalities are not found. For example,

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cats do not have a significant fragile X site on the X chromosome that is associated with mental retardation [5]. 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. However, Turner's Syndrome (XO), Klinefelter's Syndrome (XXY) and chimerism has been documented in the domestic cat. Sex chromosome aneuploidies and trisomies of small acrocentric chromosomes were typically associated with cases of decreased fertility and syndromes that displayed distinct morphological presentations. Because cat has a highly recognizable X-linked trait [7–10], *Orange*, and the X-inactivation process was recognized [11], tortoiseshell and calico male cats were the first feline suspects of chromosomal abnormalities, particularly sex chromosome aberrations. Karyotypic and now gene-based assays are common methods to determine if a cat with ambiguous genitalia [12] or a poor reproductive history has a chromosomal abnormality. Karyotypic studies of male tortoiseshell cats have shown that they are often mosaics, or chimeras, being XX/XY in all or some tissues [10,13–20]. The minor chromosomal differences that are cytogenetically detectable between a domestic cat and an Asian leopard cat are likely the cause of fertility problems in the Bengal cat breed, which is a hybrid between these two species [21]. 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 a living tissue, such as a fibroblast biopsy or whole blood for the analysis of white blood cells.

2.2. Inherited disease tests

The candidate gene approach has been fruitful in domestic cat investigations for the identification of many diseases and trait mutations. The first mutations identified were for a gangliosidosis and muscular dystrophy, discovered in the early and mid-1990's [22,23], as these diseases have well defined phenotypes and known genes with mutations that were as found in humans. Most of the common diseases, coat colors, and coat types were deciphered in the cat following the same candidate gene approach. To date, other than the muscular dystrophy mutation [22], all other mutations in the cat are autosomal.

Most of the identified disease tests in cats that are very specific to breeds and populations are available as commercial genetic tests (Table 1). Typically, diseases are identified in cat breeds, which are a small percentage of the cat population of the world, perhaps at most 10–15% in the USA [24]. However, some mutations that were found in a specific breed, such as mucopolysaccharidosis in the Siamese [25,26], were found in a specific individual and the mutation is not of significant prevalence in the breed (Table 2). These genetic mutations should not be part of routine screening by cat breeders and registries, but clinicians should know that genetic tests are available for diagnostic purposes, especially from research groups with specialized expertise, such as at the University of Pennsylvania (http://research.vet.upenn.edu/penngen). Other diseases, such as polycystic kidney disease (PKD), are prevalent, PKD in Persians is estimated at 30–38% worldwide [27–29]. Because of cross breeding with Persians, many other breeds, such as British Shorthairs, American Shorthairs, Selkirk Rex, and Scottish Folds, also need to be screened for PKD [30–32]. As PKD testing begins to become less common, as breeders remove positive cats, other genetic tests are becoming more popular, such as coat color and other disease traits (Fig. 1).

To date, most cat genetic tests have been for traits that have nearly complete penetrance, having little variability in expression, and early onset. However, some recognized mutations in cats might be considered risk factors, predisposing an individual to health

Table 1
Common commercialized DNA tests for domestic cats.

Disease/trait (alleles)	MOI[b]	Phenotype	Breeds	Gene	Mutation[d]
Agouti (*A*, *a*) [76]	AR	Banded fur to solid	All breeds	*ASIP*	c.122_123delCA
Amber (*E*, *e*) [77]	AR	Brown color variant	Norwegian forest	*MC1R*	c.250G > A
Brown (*B*, *b*, b^l) [78,79]	AR	Brown, light brown color variants	All breeds	*TYRP1*	b = c.8C > G, b^l = c.298C > T
Color (*C*, c^b, c^s, *c*) [79–81]	AR	Burmese, Siamese color pattern, full albino	All breeds	*TYR*	C^b = c.715G > T, C^s = c.940G > A, c = c.975delC
Dilution (*D*, *d*) [40]	AR	Black to grey/blue, Orange to cream	All breeds	*MLPH*	c.83delT
Gloves (*G*, *g*) [48]	AR	White feet	Birman	*KIT*	(Submitted)
Hairless (*Hr*, *hr*) [52]	AR	Atrichia	Sphynx	*KRT71*	c.816 + 1G > A
Long fur (*L*, *l*) [49,50]	AR	Long fur	All breeds[c]	*FGF5*	c.356_367insT, c.406C > T, c.474delT, c.475A > C
Rexing (*R*, *r*)	AR	Curly hair coat	Cornish Rex	*PYP2R5*	(Submitted)
Rexing (*Re*, *re*) [52]	AR	Curly hair coat	Devon Rex	*KRT71*	c.1108-4_1184del, c.1184_1185ins AGTTGGAG, c.1196insT
AB blood type (*A*, *b*) [39]	AR	Determines type B	All breeds	*CMAH*	c.1del-53_70, c.139G > A
Gangliosidosis 1 [82]	AR	Lipid storage disorder	Korat, Siamese	*GBL1*	c.1457G > C
Gangliosidosis 2 [83]	AR	Lipid storage disorder	Burmese	*HEXB*	c.1356del-1_8, c.1356_1362delGTTCTCA
Gangliosidosis 2 [23]	AR	Lipid storage disorder	Korat	*HEXB*	c.39delC
Glycogen storage dis. IV [92]	AR	Glycogen storage disorder	Norwegian forest	*GBE1*	IVS11 + 1552_IVS12-1339 del6.2 kb ins334 bp
Hypertrophic cardiomyopathy [34]	AD	Cardiac disease	Maine Coon	*MYBPC*	c.93G > C
Hypertrophic cardiomyopathy [85]	AD	Cardiac disease	Ragdoll	*MYBPC*	c.2460C > T
Hypokalemia	AR	Potassium deficiency	Burmese	*WNK4*	(Submitted)
Progressive retinal atropy [86]	AR	Late onset blindness	Abyssinian	*CEP290*	IVS50 + 9T > G
Progressive retinal atropy [87]	AD	Early onset blindness	Abyssinian	*CRX*	c.546delC
Polycystic Kidney disease [32]	AD	Kidney cysts	Persian	*PKD1*	c.10063C > A
Pyruvate kinase def.[a]	AR	Hemopathy	Several	*PKLR*	c.693 + 304G > A
Spinal muscular atrophy [88]	AR	Muscular atrophy	Maine Coon	*LIX1-LNPEP*	Gene deletion

[a] Unpublished test, presented only as abstract, paper submitted.
[b] Mode of inheritance of the non-wildtype variant.
[c] Long fur variants are more or less common depending on the breed.
[d] Not all transcripts for a given gene may have been discovered or well documented in the cat, mutations presented as interpreted from original publication.