Genetics and Precision Medicine: State of the Art Health Care for Cats!

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Dr. Lyons' doctorate degree is in human genetics from the University of Pittsburgh, Graduate School of Public Health. She spent seven years at the National Cancer Institute, Laboratory of Genomic Diversity developing genetic resources, working with early generation Bengal cats, and collecting disease and phenotypic traits for the domestic cat. In 1999, she moved to the University of California - Davis, School of Veterinary Medicine to continue research on cats, including the identification of inheritable disease mutations. She identified the DNA variant for the most common inherited disease in cats, polycystic kidney disease, and has been involved with the identification of over 20 cat DNA variants, including many involving coat colors, fur types, B blood type and other diseases. In 2013, Dr. Lyons joined the University of Missouri – Columbia, College of Veterinary Medicine as the Gilbreath-McLorn Endowed Professor of Comparative Medicine. Dr. Lyons has managed a cat colony of different breeds and species for over 20 years and has two cats or her own, Withers and Watson.

Dr. Lyons received her first Winn Feline Foundation award while at the National Cancer Institute that focused on the genetics of the Burmese craniofacial defect. The WFF and the Lyons Feline Genetics Laboratory have continued a successful partnership, identifying important disease mutations such as Polycystic Kidney Disease, Bengal and Persian retinal degeneration, and blood group, as well as completing cat population genetic studies. Winn Feline Foundation was one of the first to sponsor the cat DNA array studies and the 99 Lives Cat Genome Sequencing Project, which now has over 100 cats and many wild felids in the database of cat genomes.

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The genetic and genome resources available for health studies of the domestic cat are becoming sufficiently robust and cost efficient. The sequencing of a cat's entire genome can now be completed for under $2,000 USD. The 50-hour and now the 26-hour genome efforts have demonstrated how genome medicine in humans can be applied to health management for acute care patients with time-critical morbidity and mortalities. Although the availability of the bioinformatics infrastructure and speed are not yet available in cats as available for humans, the DNA variant database developed by the 99 Lives Cat Genome Sequencing Initiative has proven valuable. Developed from a variety of cats from diverse populations and breeds, including cats with no known and known genetic health problems, the cat variant database supports the identification of DNA variants that are rare and causal for health conditions suspected to have a genetic component. Two whole genome sequencing (WGS) studies have already identified three DNA variants in cats that are associated with progressive retinal atrophy in Persian cats, the bobbed tail of the Japanese Bobtail breed, and Congenital Myasthenic syndrome in Devon rex and Sphynx – related cats.

Precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle. President Obama announced the Precision Medicine Initiative® (PMI) in his State of the Union address in 2015. Most medical treatments have been designed for the "average patient". *Precision Medicine* gives clinicians tools to better understand the complex mechanisms underlying a patient's health, disease, or condition, and to better predict which treatments will be most effective. Overall, an individual's specific genetic make-up will become an intricate part of their standard health care. Can cats have *Precision Medicine* too?

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. The clinical descriptions and phenotypes of each of these diseases and traits have been curated at the Online Mendelian Inheritance in Animals (OMIA) website (http://omia.angis.org.au/home/), which is an invaluable resource comparison of the phenotypes across 2216 animal species. These known variants and newly identified DNA variants can be genotyped rapidly and cost effectively in panels that appropriate for breeds, populations or in feline patients as part of wellness care. The vigilance of veterinarians and the collaboration with geneticists could lead to the rapid discovery of undiagnosed genetic conditions in cats, which hopefully lead to more effective and proactive treatments.

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. Once cats became domesticated, some of the first noticeable genetic alterations conferred phenotypic variations, such as fur length, fur type, coat colors, and coat patterns. If you know your alphabet, you can basically remember most of the phenotypic genes and loci that affect the appearance of a cat.

A few of the DNA variants listed in **Table 1** may not be considered "good" by current cat breeding standards. Indeed, 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*). The Manx DNA alterations are lethal *in utero* in the homozygous state and many Manx cats have issues with lameness, incontinence and constipation. The discovery of the *Tailless* variants has also revealed that Japanese Bobtail cats do not have DNA changes in the same gene and that the PixieBob breed has Manx and Japanese Bobtail genetic contributions. Many argue that the hairless phenotypes are "too unnatural" for a cat and they can suffer from potential hypothermia and sun burn. Dwarfism is another controversial

phenotype, propagated as the Munchkin cat breed. However, the dwarfism breed and the DNA variant have not been scientifically documented and health concerns not yet identified. Other well-known health concerns are the Scottish Fold phenotype, which is associated with osteochondrodysplasia. Many breeders seem to think that osteochrondrodysplasia occurs only in the homozygous cat. Likely, some disease in heterozygote cats manifestations sub-clinically. In addition, dominant *White* is associated with deafness and increased risks of melanomas due to depigmentation and UV-exposure. Deciphering the gene alleles associated with Scottish Folds and dominant *White* cats will likely help us to understand the basic biology of the genes and the role of genetic modifiers that influence the undesired and linked health concerns.

The genetically characterized diseases and health concerns for specific cat breeds 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-associated and private laboratories. These DNA variants should be monitored by cat breed registries and become the cat DNA alterations that are most familiar to veterinary practitioners as they are useful diagnostics.

Some DNA variants that were found in a specific breed, such as mucopolysaccharidosis Type VI in the Siamese, were found in a specific individual and the variant is not of significant concern in the breed. **Table 3** lists cat DNA alterations identified in random bred cats and disease conferring variants that have not propagated within a breed. These genetic variants 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. If similar conditions are suspected in cats, 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 and 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 orders.

Domestic cats have 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**.** 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. The alignment of genes on chromosomes in cats is very similar to the genomic organization in humans. Humans have their genes distributed onto 22 autosomes, therefore only a small number of changes are required to rearrange the same genes onto 18 autosomes, as found in cats. Most mammals have ~21,000 genes residing on their chromosomes and the coding portion of these genes is conserved across species. Many of the trait and disease mutations identified to date have been in exons, the coding portions of genes. However, all species are discovering that the regulatory elements in the non-coding portions of genes, such as introns and untranslated regions, harbor > 60% of causal mutations for diseases and trait.

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 one month. Currently, whole genome sequencing is becoming the standard of health care for genetic profiling of cancers, which can dictate the proper selection of chemotherapies based on DNA mutations of the tumor. 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. 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 but requires greatly better definition in others. Likely, whole genome sequencing will become part of the

health care package for human health. Recently, the $1,000 genome cost has been reached for humans, shortly this technology will be adapted for other species. For cats, currently whole genome sequencing is being used to investigate diseases and traits that are known to be heritable, and 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.

A cooperative approach that supports small laboratories that do not have vast resources and skills, particularly for bioinformatics, is allowing new investigators, particularly with veterinary backgrounds, to participant in DNA variant discovery for health concerns. Thus, the concept of a low cost, centralized genome sequencing effort has developed for cat researchers – the 99 Lives Cat Genome Sequencing Initiative. The 99 Lives project has a centralized resource with genome sequences produced of similar quality and similar techniques to facilitate variant discovery. The resource is expected to help develop a higher density DNA array for complex diseases studies in common cats – regular house cats and to support researchers with variant discovery and for evolutionary studies. The *99 Lives* Cat Genome Sequencing Initiative (http://felinegenetics.missouri.edu/ninety-nine-lives) has been launched to meet the same standard in health care for cats as for humans. The sporadic or idiopathic conditions will slowly be determined to have individual specific genetic causes, leading to highly specific personalized medicine for our companion animals.

Table 1 The phenotypic traits of the domestic cat.

Disease / Trait (alleles) OMIA Entry	MOI‡	Phenotype	Gene	Gene Name	Mutation
Agouti (A^+, a, A^{Pbe})[1, 2] 000201-9685	AR	Banded fur to solid	*ASIP*	*Agouti-signaling protein*	c.122_123delCA; Pbe haplot
Brown (B^+, b, b^l)[3, 4] 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)[4-6] 000202-9685	AR	Burmese, Siamese color pattern, full albino	*TYR*	*Tyrosinase*	c^b = c.715G>T, c^s = c.940G> = c.975delC
Dilution (D^+, d)[7] 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, e^r) – Amber[8] 001199-9685	AR	Brown/red color variant	*MC1R*	*Melanocortin receptor 1*	c.250G>A; c.439TCT
Fold (Fd, fd^+)[9] 000319-9685	AD	Ventral ear fold	*TRPV4*	*Transient Receptor Potential cation channel, subfamily V, member 4*	c.1024G>T
Gloves (G^+, g)[10] 001580-9685	AR	White feet	*KIT*	*KIT*	c.1035_1036delinsCA
Hairless (Hr^+, hr)	AR	Atrichia	*KRT71*	*Keratin 71*	c.816+1G>A
Inhibitor (I, i^+) 001583-9685	AD	Absence of phaeomelanin	*unknown*	*unknown*	*unknown*
Japanese Bobtail (J, j^+)[11]	AD	*Kinked tail*	*HES7*	*Hairy and Enhancer of Split family, transcription factor 7*	c.5A>G
Kurl (K, k^+) 000244-9685	AD	*Rostral curled pinnea*	*unknown*	*unknown*	*unknown*
LaPerm 000245-9685	AD	Curly hair coat	*unknown*	*Unknown*	*unknown*
Longhair (L^+, l)[12, 13] 000439-9685	AR	Long fur	*FGF5*	*Fibroblast growth factor 5*	c.356_367insT, c.406C>T c.474delT, c.475A>C
Lykoi	AR	Absent undercoat	*unpub*	*unpub*	unpub
Manx (M, m^+)[14] 000975-9685	AD	Absence/short tail	*TBOX*	*T – box*	c.998delT, c.1169delC, an c.1199delC, c.998_1014dup17delGCC
Orange (O, o^+)	X linked	Change in pigment hue	*unknown*	*unknown*	*unknown*
Peterbald	AD	Hairless, brush coat	*unknown*	*unknown*	*unknown*

001201-9685					
Polydactyla (Pd, pd^{+})[15] 000810-9685	*AD*	Extra toes	*SHH*	*Sonic hedgehog*	c.479A>G, c.257G>C, c.481
Rexing (R^{+}, r)[16] 001684-9685	AR	Curly hair coat	*LPAR6*	*Lysophosphatidic acid receptor 6*	c.250_253delTTTG
Rexing (Re^{+}, re)[17] 001581-9685	AR	Curly hair coat	*KRT71*	*Keratin 71*	c.1108-4_1184del, c.1184_1185insAGTTGGA(c.1196insT
Rexing (R^{S}, r^{s+})[18] 001712-9685	AD	Curly hair coat	*KRT71*	*Keratin 71*	c.445-1G>C
Spotting (S, s^{+})[19] 000214-9685	Co-D	Bicolor / van white	*KIT*	*KIT*	7125ins FERV1 element
Tabby(T^{M}, t^{b})[20] 001429-9685	AR	Blotched/classic pattern	*TAQPEP*	*Transmembrane aminopeptidase Q*	S59X, T139N, D228N, W84
Ticked (T^{a}, t) 001484-9685	AD	No Tabby pattern	*unknown*	*unknown*	*unknown*
White (W, w^{+})[19] 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. A "+" implies the wild type allele when known. In reference to the mutant allele, AD implies autosomal dominant, AR implies autosomal recessive, co-D implies co-dominant. OMIA: Online Mendelian Inheritance in Animals (http://omia.angis.org.au/home/) entries provides links to citations and clinical descriptions of the phenotypes and the diseases. Presented citations are for the causative variant discovery.

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

Disease / Trait (alleles) OMIA Entry	MOI‡	Phenotype	Gene	Gene Name	Mutation
AB Blood Type (A^+, AB, b)[21, 22] 000119-9685	AR	Determines Type B	*CMAH*	*cytidine monophospho-N-acetylneuraminic acid hydroxylase*	c.1del-53_70, c.139G>A
Craniofacial Defect[23]	AR	Craniofacial Defect	*ALX1*	*Aristaless-Like Homeobox 1*	c.496delCTCTCAGGACTG
Gangliosidosis 1[24] 000402-9685	AR	Lipid storage disorder (GM1)	*GLB1*	*Galactosidase, beta 1*	c.1457G>C
Gangliosidosis 2[25] 01462-0985	AR	Lipid storage disorder (GM2)	*HEXB*	*Hexominidase B*	c.1356del-1_8, c.1356_1362delGTTCTCA
Gangliosidosis 2[26] 01462-0985	AR	Lipid storage disorder (GM2)	*HEXB*	*Hexominidase B*	c.39delC
Glycogen Storage Dis. IV[27] 000420-9685	AR	Glycogen storage disorder(GSD)	*GBE1*	*Glycogen branching enzyme 1*	IVS11+1552_IVS12-1339 del6.2kb ins334 bp
Hypertrophic Cardiomyopathy[28] 000515-9685	AD	Cardiac disease (HCM)	*MYBPC*	*Myosin binding protein C*	c.93G>C
Hypertrophic Cardiomyopathy[29] 000515-9685	AD	Cardiac Disease (HCM)	*MYBPC*	*Myosin binding protein C*	c.2460C>T
Hypokalemia[30] 001759-9685	AR	Potassium deficiency (HK)	*WNK4*	*WNK lysine deficient protein kinase 4*	c.2899C>T
Progressive Retinal Atropy[31] 001244-9685	AR	Late onset blindness (rdAC)	*CEP290*	*Centrosomal protein 290kDa*	IVS50 + 9T>G
Progressive Retinal Atropy[32] 000881-9685	AD	Early onset blindness (rdy)	*CRX*	*Cone-rod homeobox*	c.546delC
Polycystic Kidney Disease[33] 000807-9685	AD	Kidney cysts (PKD)	*PKD1*	*Polycystin 1*	c.10063C>A
Pyruvate Kinase Def.[34] 000844-9685	AR	Hemopathy (PK Deficiency)	*PKLR*	*pyruvate kinase, liver, RBC*	c.693+304G>A
Spinal Muscular Atrophy[35] 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. A "+" implies the wild type allele when known. In reference to the mutant allele, AD implies autosomal dominant, AR implies autosomal recessive, co-D implies co-dominant. OMIA: Online Mendelian Inheritance in Animals (http://omia.angis.org.au/home/) entries provides links to citations and clinical descriptions of the phenotypes and the diseases. Presented citations are for the causative variant discovery.

Table 3 Uncommon mutations for inherited domestic cat diseases[†].

Disease / OMIA Entry	OMIA Entry	Gene	Mutation[‡]
11b-hydroxylase Def. (Congenital Adrenal Hypoplasia)[36]	001661-9685	*CYP11B1*	Exon 7 G>A
Congenital Myasthenic Syndrome[37]		*CLCN1*	c.1930+1G>T
Dihydropyrimidinase Deficiency[38]	001776-9685	*DPYS*	c.1303G>A
Factor XII Deficiency[39]	000364-9685	*FXII*	c.1321delC
Fibrodysplasia Ossificans Progressiva	000388-9685	*unpub*	unpub
Gangliosidosis 1[40]	000402-9685	*GLB1*	c.1448G>C
Gangliosidosis 2[41]	001462-9685	*HEXB*	c.1467_1491inv
Gangliosidosis 2[42]	001462-9685	*HEXB*	c.667C>T
Gangliosidosis 2[27]	001427-9685	*GM2A*	c.390_393GGTC
Hemophilia B[43]	000438-9685	*F9*	c.247G>A, c.1014C>T
Hyperoxaluria[44]	000821-9685	*GRHPR*	G>A I4 acceptor site
Hypothyroidism	000536-9685	*unpub*	unpub
Lipoprotein Lipase Deficiency[45]	001210-9685	*LPL*	c.1234G>A
Mucolipidosis II[46]	001248-9685	*GNPTAB*	c.2655C>T
Mannosidosis, alpha[47]	000625-9685	*LAMAN*	c.1748_1751delCCAG
Mucopolysaccharidosis I[48]	000664-9685	*IDUA*	c.1107_1109delCGA; c.1108_1110GAC
Mucopolysaccharidosis VI[49]	000666-9685	*ARSB*	c.1427T>C
Mucopolysaccharidosis VI[50, 51]	000666-9685	*ARSB*	c.1558G>A
Mucopolysaccharidosis VII[52]	000667-9685	*GUSB*	c.1052A>G
Muscular Dystrophy[53]	001081-9685	*DMD*	900bp del M promoter -exon 1
Niemann-Pick C Type 1[54]	000725-9685	*NPC1*	c.2864G>C
Niemann-Pick C Type 2[55]		*NPC2*	c.82+5G>A
Polydactyly[15]	000810-9685	*SHH*	c.479A>G, c.257G>C, c.481A>T
Porphyria (congenital erythropoietic)[56]*	001175-9685	*UROS*	c.140C>T, c.331G>A
Porphyria (acute intermittent)[57]*	001493-9685	*HMBS*	c.842_844delGAG, c.189dupT, c.250G>A, c.445C>T
Vitamin D Resistant Rickets[58]	000837-9685	*CYP27B1*	c.223G>A, c.731delG
Vitamin D Resistant Rickets[59]	000837-9685	*CYP27B1*	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 (http://omia.angis.org.au/home/) entries provides links to citations and clinical descriptions of the phenotypes and the diseases. Presented citations are for the causative variant discovery.

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