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Quick guide

Cats

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What makes a cat? 'Cat' is one of the first one hundred words children learn. Cats are familiar as pets, numbering some 60 million in the US, and five times that many in the world. Cat domestication is young compared to dogs and barnyard animals, less than 6000 years old. Descended from the African wildcat *Felis sylvestris*, house cats are first a companion animal, but they were initially bred as an agricultural defense against rodents, and then worshipped as a deistic symbol in Egyptian religion, morphing to a dark omen of evil spirits and witchcraft by the middle ages. Domestic cats of today derive from generations of artificial selection for coat color appearance and behavior that has led to forty-odd cat breeds, revered and proudly displayed in fancy cat exhibitions across the globe. Feral cats, released to form semi-wild social communities in urban and rural settings, are at best nuisances and at worst vilified predatory pests to fragile birds and wildlife in conservation-minded Europe, Australia and New Zealand.

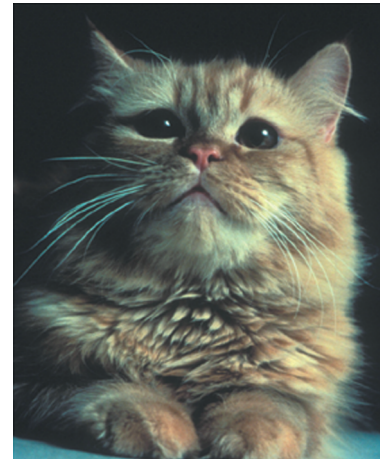
Domestic cats carry in their genomes the majesty and resilience of their fantastically successful wild relatives, the 36 living species of the Felidae family. The cat family, one of eight within the order Carnivora, contains species with remarkable size variance (from the 3 lb South African black footed cat to the 700 lb Siberian tiger), exquisite predatory acumen and complex reproductive and social behavior. The great roaring cats of the *Panthera* genus sit atop the trophic chain in every ecosystem they occupy and have fascinated humankind since history began. The 36 Felidae species are arguably the most successful and charismatic of all carnivore species occupying parallel

ecological niches on every continent except Australia and the poles. Wild cats dominate their habitat but require vast expanses to survive, which explains the tragic depredation such that every species of Felidae, except the domestic cat, is considered either endangered or threatened in the wild today by CITES, IUCN Red Book and other monitors of the world's most endangered species.

Why are cats of interest in biology, medicine and genomics? Cats have been studied for centuries by anatomists, physiologists, behaviorists and now geneticists. There are lots of them, small and easy to keep in the laboratory. Whether we love cats or hate them, biology has learned much from studies of their comparative anatomy, comparative physiology (notably neurology) and behavior. For many biological sub-disciplines, the 36 cat species are considered as three groups: large, medium and small, a testament to their amazing similarity.

The exception is reproduction, where each species has evolved exquisite co-adapted strategies for ovulation, hormone level regulation, sperm production, estrous incidence, mating preference and social organization. Scrutiny by behavioral ecologists has provided a rich literature of distinctive reproductive parameters for several cat species, facilitating advances in assisted reproduction such as artificial insemination, cryo-preservation, embryo transfer, *in vitro* fertilization and the first cloning of a domestic cat in 2002. The advanced stage of reproductive assessment will one day soon lead to feline embryonic stem cells, transgenic and gene knockout cats, and protocols for stem cell and gene therapy trials.

One of the most powerful biomedical models for cats involves the interaction of deadly infectious agents and the cat host's genome. Domestic cats first gave us feline leukemia virus, which allowed the discovery of



A Persian breed domestic cat. (Photo courtesy of M. Calingo).

scores of 'oncogenes' in the 1970s and 1980s. When homologous human oncogenes were rapidly discovered thereafter, their misfiring in signal transduction pinpointed the molecular basis for many aggressive cancers. More recently, feline immunodeficiency virus (FIV), a first cousin of HIV, was discovered in house cats as the cause of a depletion of the CD4 T-cell subset that is a prelude to immune system collapse and pathology, the only naturally occurring model of AIDS. Interestingly, over eight free-ranging wild species of Felidae are infected with their own species-specific FIV strain (based on FIV gene sequence monophyly) that in most cases seems to be attenuated by historic selection of genetically resistant survivors in today's wild places. The devastating SARS human coronavirus has a feline counterpart that causes a deadly feline infectious peritonitis (FIP) syndrome in domestic cats. An outbreak of FIP in a genetically uniform African cheetah colony led to 100% morbidity and 60% mortality, emphasizing the sensitivity of genetically inbred hosts to viral outbreaks.

Cats and their wild relative have given some sobering lessons about emerging virus outbreaks. In the mid 1970s, a feline pan-leucopenia virus cultivated in a cat vaccine factory abruptly jumped from cats to dogs, producing a hyper-virulent

strain in puppies that within a few months caused widespread puppy mortality across the world. Payback from the dogs came when a strain of canine distemper, endemic in the pet dogs of Masai tribesman in Tanzania, jumped to hyenas and then to African lions, killing a third of the huge lion population of Serengeti National Park in a six month interval in 1994.

Add to the list of verified cat-specific agents: alpha-herpesvirus, toxoplasmosis, cryptococcus, plague, Q-fever, chlamydiosis and rotavirus infections, ehrlichiosis, calicivirus infection, poxvirus infection and mycobacteriosis. Cats are also highly resistant to anthrax, with obvious implications. All these infections, and more, could prove valuable to biomedical research, providing we have a better working knowledge of the innate and adaptive immune system of cats.

Domestic cats and dogs enjoy more medical scrutiny than any species except humans. The world's veterinary schools produce thousands of practitioners each year, providing extensive documentation of genetic and chronic diseases with relevance to human maladies. The result is a comprehensive veterinary literature, which has described some 258 feline genetic diseases (<http://www.angis.org.au/Databases/BIRX/omia/>). These disease models offer, not only insight into disease development, but opportunities for better diagnostics and treatment experimentations.

What will we learn from a feline genome project? In August 2004, The US National Human Genome Research Institute (NHGRI) announced its decision to support sequencing of the domestic cat genome, along with those of seven other species: elephant, armadillo, tenrec, common shrew, guinea pig, hedgehog and rabbit. These species were chosen to complement those already selected for whole genome sequencing (human, mouse, rat, cow, chimpanzee, macaque,

opossum and platypus) and to reflect the diversity among the 4500 living species of mammals as a first step in annotating the human genome's largely uninterpreted coding, regulatory and evolutionary conserved sequences. The cat offers the promise of a second carnivore species (in addition to the dog, which shares a common ancestor with cats dating back to approximately 60 million years ago) to improve human genome annotation, as well as to complement the biomedical and genomic discoveries that make the feline genome attractive.

Genome evolution in mammals appears to proceed at two very different rates. The common default rate of chromosomal exchange is very slow and deliberate, so that the genome organization can be inferred for the common ancestor of all primates, carnivores and placental mammals. But a more rapid mode of genome rearrangement is seen in some lineages, such as gibbons, owl monkeys, dogs, bears and murid rodents, the genomes of which appear to have been re-shuffled several times relative to the ancestral form. Cats and humans both have genomes in the primitive, un-rearranged form, so the cat provides a good opportunity to study the constraints on genome organization that have characterized the 105 million year old mammalian radiations. The conserved genome of the cat is retained in the other 36 Felidae species, as well as most of the 246 species of the Carnivora order, the only reshuffled exceptions occurring in the dog and bear families.

What can we expect after the cat genome sequence becomes available? Many areas of biological and medical research will benefit from the projected cat genome sequence. Human genome interpretation and annotation will be augmented by, on average, a single variant for each of its three billion base pairs. Cats will enjoy genomic tools for inspection of

feline hereditary disease, as well as the discovery of candidate gene variants that may explain evolved genomic defenses of infectious disease that threaten cats and man. Evolutionary biologists will identify specific genes contributing to survival and species formation as unabridged gene/sequence maps narrow the search for adaptations. The observed constraints on genome re-organization will become a challenge for inferring the footprints of evolutionary steps that led to the modern cat species. An increased and informed database of mechanistic developmental specializations will add yet another reason to conserve the surviving cat species that are the keystone of species and habitat conservation projects, from cheetahs in Namibia, to tigers in India and the Russian far east, to lions in east Africa and jaguars in the Amazon.

Where can I find out more?

- <http://www.angis.org.au/Databases/BIRX/omia/>
- <http://home.ncifcrf.gov/ccr/igd/>
- http://www.genomenewsnetwork.org/resources/sequenced_genomes/genome_guide_p1.shtml
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