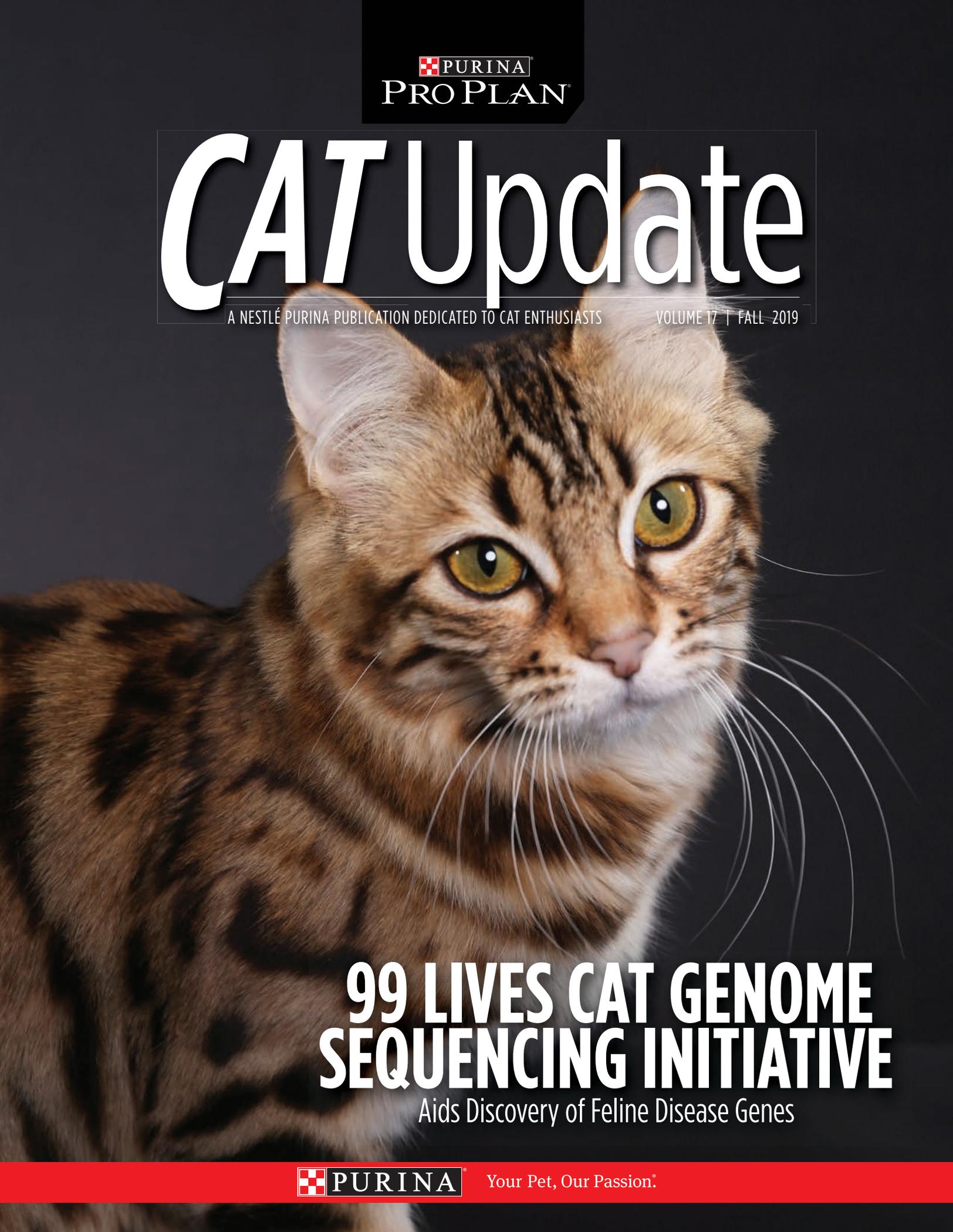


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CAT Update

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99 LIVES CAT GENOME SEQUENCING INITIATIVE

Aids Discovery of Feline Disease Genes

 PURINA

Your Pet, Our Passion.

99 Lives Cat Genome Sequencing Initiative

HELPS TO ADVANCE DISCOVERY OF DISEASES AND TRAITS

“We found that glitter is caused by a mutation in a gene called fibroblast growth factor receptor 2, which regulates the growth and structural composition of hair in cats and other mammals.”

Chris Kaelin, PhD, senior scientist at Stanford University and HudsonAlpha Institute

Research of feline genetic diseases and traits got a huge boost in 2015 when the [99 Lives Cat Genome Sequencing Initiative](#) was founded. The purpose was to build an in-depth, accessible genetic database of domestic and wild cat species that researchers could use to investigate heritable diseases. Many studies have benefited from having a handy source of DNA.

Geneticist Leslie Lyons, PhD, the Gilbreath McLorn Endowed Pro-

fessor of Comparative Medicine at the University of Missouri, who began the 99 Lives Initiative, says, “The idea was to include all breeds and cats from around the world — those that are healthy as well as those with health concerns.”

Thus far, donated DNA samples from more than 200 domestic cats — including 37 pedigree cat breeds and crossbreeds — and 21 wild cats representing 15 wild cat species have been whole-genome sequenced.



CH Jungletrax Orange Fanta C, a glittered brown-spotted tabby female Bengal kitten, was bred and is owned by Anthony Hutcherson.

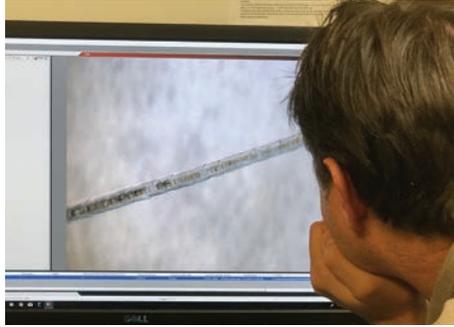
“Currently, there are 56 principle investigators at 43 institutions, companies and zoos contributing to and using data to study about 200 diseases and phenotypes,” Dr. Lyons says. “There are about 52 cats involved with cardiac disease studies, plus there are 21 neurological studies, four behavior studies, five urinary studies, and many others as well.”

Research tied to the 99 Lives Initiative stood out among the feline presentations at the 10th International Conference on Canine and Feline Genetics and Genomics held in May 2019 in Bern, Switzerland. The scientific meeting, attended by 200 research scientists and graduate students from 20 countries, was sponsored by Purina.

At the Bern conference, Chris Kaelin, PhD, senior scientist at Stanford University and Hudson-Alpha Institute, told how his team tapped into the 99 Lives Initiative to find the mutation that causes a desirable coat trait in Bengal cats called “glitter.” They also added to what was known about a distinctive Bengal trait called “charcoal.”

Bengals are known for the beauty of their ornate color coat patterns reminiscent of the spotted coat of the Asian leopard cat that was crossed with domestic cats 35 years ago to create the popular breed. In some Bengals, a bonus sparkling or iridescence – the glitter effect – adds a lovely sheen to the coat. Meanwhile, the charcoal trait gives some Bengal cats markings like Zorro, with a white goggle look around the eyes and a cape effect that extends down their back.

“We found that glitter is caused by a mutation in a gene called fibroblast growth factor receptor 2, which regulates the growth and structural composition of hair in cats and other mammals,” Dr. Kaelin says. “Extending work done previously by Dr. Lyons and her colleagues, we showed that the charcoal allele



Dr. Chris Kaelin, studying a strand of glittered hair coat, identified the mutation for the coat color anomaly using data from the 99 Lives Cat Genome Sequencing Initiative.

was independently introduced by multiple, different Asian leopard cats during Bengal breed development. The Asian leopard cat allele works less efficiently when swapped in a domestic cat and the result is a dark, Zorro-like appearance.”

A Bengal breeder who has donated more than 100 DNA samples to genetic studies, Anthony Hutcherson of Jungletrax cattery in Port Tobacco, Maryland, helped Dr. Kaelin discover the glitter variant. His cat, RW SGC Jungletrax Flowmaster, carried the gene insertion and was part of the study.

“When ‘Flowmaster’ sits in the sunshine, he glows like he’s plugged into an electric outlet,” says Hutcherson, a member of the board of directors of Winn Feline Foundation and The International Cat Association. “Glitter comes from a single domestic cat, Millwood Tory of Delhi, used to create the Bengal breed. A homeless cat in India added one of the most beautiful and unique traits in our breed.”

Winn Feline Foundation, a non-profit organization that supports exclusively feline medicine research, has funded the 99 Lives Cat Genome Sequencing Initiative since the beginning, as well as its predecessor, the 9 Lives Cat Genome Sequencing Project. Both have evolved from completion of the feline genetic map in the fall of 2005, which was developed using an Abyssinian cat



Purina has sponsored the International Conference on Canine and Feline Genetics and Genomics since its beginning in 2002. The 10th meeting of the group of research scientists was held in May 2019 in Bern, Switzerland.



RW BW SGC SimplyBlessed Arctic Summer, bred and owned by Beth and Lori Beary, is the first longhaired Bengal to be named a Supreme Grand Champion by The International Cat Association.

named “Cinnamon.” In 2005 there were about 1,680 markers.

“Our DNA array has 63,000 markers, and many have been mapped in cat pedigrees,” Dr. Lyons says. “The cat genome is now one of the best for any species, except mouse and man.”

“The 99 Lives Initiative makes it quicker, easier and cheaper to find DNA variants that cause significant disease,” says Vicki Thayer, DVM, DABVP (feline), former executive director of Winn Feline and current member of the board of directors. “Over the past three decades Winn Feline has funded genetic feline diseases, there certainly have been a lot of ‘wins’ along the way.”

Whole-genome sequencing enables an individual cat’s entire genetic blueprint to be analyzed for changes to the genetic code. The feline genome is made up of 2.5 billion coding units, consisting of four nucleotides denoted by the letters A, T, C and G. These differences are then compared to see if any may be linked to a certain disease or trait.

Among the successes that have come from researchers using the 99 Lives feline databank, Dr. Lyons, who also presented at the Bern genomics conference, gives credit to the discovery of different gene mutations for progressive retinal atrophy in Persians, Bengals and South African black-footed cats, myopathy in Devon Rex, lymphadenopathy in British Shorthairs, and the tail mutation in the Japanese Bobtail.

Work underway involves a complicated study to identify cats at risk for feline infectious peritonitis (FIP), with a goal of ultimately helping clinicians determine whether cats exposed to the virus will develop disease. The most important viral disease in cats under 3 years of age, FIP is caused by a mutant form of a highly contagious but common virus in cats’ intestinal tract, feline enteric coronavirus (FECV). The mutation that causes FIP is believed to occur in individual cats that cannot fight off the new type of infection, commonly affecting kittens and cats with weak immune systems.

EARLY PRA DISCOVERIES

Among her own breakthroughs, Dr. Lyons discovered the different autosomal recessive gene mutations causing progressive retinal atrophy (PRA) in Bengals and Persians, projects that took place over a decade and through her moving from the University of California-Davis to her current position at the



**99 LIVES CONSORTIUM
FELINE GENETIC DISCOVERIES**

Disease or Trait	Status
Progressive retinal atrophy (PRA) in Bengals	DNA test available via the University of California-Davis Veterinary Genetics Laboratory
PRA in Persians	DNA test available via the University of California-Davis Veterinary Genetics Laboratory & research published in BMC Genomics
PRA in South African black-footed cats	Research published in Scientific Reports in 2017 & in 2018
Niemann-Pick Type C1 (neurological condition) in American Shorthairs	Variant identified & research published in March 2017 in the Journal of Veterinary Internal Medicine
Japanese Bobtail short-tail gene mutation	Variant identified & research published in BMC Genomics
Retinal degeneration in black-footed cat (<i>felis nigripes</i>)	Variant identified
Lil' Bub celebrity cat with osteopetrosis and polydactylism causal mutations identified	Variants identified & research published online in 2019 in bioRxiv
Dwarfism in Munchkin cat breed	Variant identified
Macular degeneration	Variant identified
Hydrocephalus in Orientals and Toygers	DNA test available
Amyloidosis in Abyssinians	Variants identified
Chediak-Higashi syndrome (albinism) in Persians	Variant identified
Epilepsy	Variants identified

“With PRA, I would like to be at the point where we could correct vision by putting a corrected version of the gene into the photoreceptor of the eye.”

Leslie Lyons, PhD, Gilbreath McLorn
Endowed Professor of Comparative
Medicine, University of Missouri

University of Missouri. An inherited eye disorder, PRA causes degeneration of the retina, eventually leading to blindness. Located at the back of the eye, the retina takes the light gathered and focused by the eye's rods and cones and converts it into electrical nerve signals, sending it on to the optic nerve and then the brain for interpretation.

An early-onset PRA in Persians progresses rapidly in kittens and causes blindness by 12 to 16 weeks of age. In Bengals, the disease occurs later and is slower progressing, with vision problems starting around 4 to 5 months of age and resulting in severe visual impairment.

Bengal breeders Beth and Lori Bearry of Simply Blessed Bengals in Jackson, California, recall visiting the University of California-Davis Veterinary Medical Teaching Hospital with their 6-month-old kitten named Idle Chatter and thinking he may have developed cataracts because they noticed his eyes glowed. "He would pace back and forth as evening fell," Beth Bearry says. "When it got dark outside, he would find a safe place in our house to stay until morning."

Veterinary ophthalmologists suspected that Idle Chatter could have PRA. "We were heartbroken when he was diagnosed at 8 months old and then went blind between 12 and 14 months old," says Beth Bearry.

Dr. Lyons began studying Idle Chatter's genetics. First, she and her team ensured that the cat's PRA was not due to a dietary taurine deficiency or antibiotics, both of which can cause blindness. Working with Beth and Lori Bearry, through repeat breedings of the tom and queen, they found that some of the kittens became blind, indicating an inherited link.

"We recognized this as a recessive trait, but then we needed to know how and why PRA developed in Bengals," Dr. Lyons says.

The gene variant discovery finally came in 2013 — through the 9 Lives Cat Genome Sequencing Project. Dr. Lyons, who had now moved her laboratory to the University of Missouri, had access to the whole-genome information of 10 cats. "We sequenced the DNA of a trio of cats and performed a comparative, genome-wide association study," she says. "This narrowed the PRA defect down to one chromosome and one region on that chromosome."

Although several variants were possible in Bengals, three gene mutations discovered previously in Abyssinians and Persians were not it. Neither was the first DNA variant they studied in Bengals. "A blind cat showed us a second variant in a gene never known before to cause blindness, which turned out to be key in Bengals," Dr. Lyons says.

[Findings of the gene variants for PRA in Bengals and Persians were developed into genetic tests at the University of California-Davis Veterinary Genetics Laboratory.](#)

FELINE DNA NEEDED FOR 99 LIVES CAT GENOME SEQUENCING INITIATIVE



The research team at the University of Missouri is seeking DNA samples from 16 cat breeds and from cats with particular feline diseases. Breeds in which DNA is needed are: American Bobtail, Balinese, Bombay, Burmilla, Cornish Rex, Chausie, Exotic Shorthair, Khamomanee, Kurilian Bobtail, Manx, Norwegian Forest Cat, Russian Blue, Singapura, Somali, Thai, and Turkish Van.

They are looking for DNA from cats diagnosed with inherited cancers: lymphoma, fibrosarcoma, squamous cell carcinoma, melanoma, and mammary cancer. They also are seeking DNA from these cats with unusual coat phenotypes: Peterbald, Don Sphynx and American Wirehair.

For information contact Dr. Leslie Lyons at the University of Missouri at lyonsla@missouri.edu. For information about the cancer studies, contact Dr. Wesley Warren at warrenwc@missouri.edu.



Jungletrax Scion Affinity Marquee is a Bengal male bred by Anthony Hutcherson.

Cat breeders have been able to order genetic testing kits since 2015, enabling them to identify carriers and breed away from the disease. In an autosomal recessive disease, an affected cat inherits the gene mutation from both the queen and tom, which are carriers and have one copy of the PRA variant.

All of the cats at the Simply Blessed Bengals cattery have been DNA tested for PRA. “We have never had any more PRA resulting in blind cats or kittens,” says Beth Bearry. “We are careful to only breed carrier cats to non-carriers, and we test the litter if we want to keep a cat in our breeding program.”

The hope of being able to breed away from genetic diseases is the crux of the 99 Lives Initiative. “The long-term goal is to be able to use precision medicine to treat cats with diseases in which the gene mutation is known,” Dr. Lyons says. “With PRA, I would like to be at the point where we could correct vision by putting a corrected version of the gene into the photoreceptor

of the eye. This would take over and make the right proteins and do what is necessary for normal vision. We are just at the tip of the iceberg.”

Reflecting on the progress that has been made thanks to the 99 Lives Initiative, particularly related to how it impacts cat breeders, Hutcherson, who attended the genomics conference in Bern, says, “It’s thrilling to see advances in feline health understanding. I appreciate that these advances are a direct result of collaborations between research scientists like Dr. Kaelin and Dr. Lyons, cat enthusiasts like me, funding organizations like Winn Feline Foundation, and pet industry leaders like Purina.” ■

Purina appreciates the support of the Winn Feline Foundation, and particularly Vicki L. Thayer, DVM, DABVP (feline), former executive director and current member of the board of directors, in helping to identify this topic for the *Cat Update*.

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