



# THE WINN FELINE FOUNDATION

For the Health and Well-Being of All Cats

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Winn Feline Foundation Announces Five Grants Awarded in Partnership with the  
Miller Trust for a Total of \$116,500  
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## **MT08-001: SNP Analysis in Siberian Cats with HCM**

*Robert A. Grahn; University of California, Davis. \$18,086*

Hypertrophic cardiomyopathy (HCM) is the dominant inherited cardiac disorder in domestic cats. Genetic mutations for this disease have been identified in both Maine Coon and Ragdoll cats. HCM has also been identified in the American Shorthair, Devon Rex, Sphynx, Bengal and Siberian breeds, among others. A causative mutation has not been identified in these breeds. Moreover, the known mutation is not completely concordant with disease presentation in Maine Coons. Because the fecundity of affected cats tends to be decreased, multigenerational pedigrees with enough statistical power to find linkage are difficult to obtain. Similarly, candidate gene approaches depending upon educated guesses and negative results do not eliminate a candidate, but merely reflect an inability to detect a causal mutation. The current study conducts case-control research on three breeds of cats: Maine Coon, Ragdoll, Siberian. Proof of principle will be established with limited numbers of known affected and control samples from Maine Coons and Ragdolls. An extensive data set for Siberians, a breed with HCM but no associated causal mutation, will be analyzed against feline single nucleotide polymorphisms (SNPs) identified in or near seven genes known to have mutations that result in human HCM. These include the identified feline HCM mutations in *MYBPC3*. Either of two results is possible; 1) SNP haplotypes associated with affected cats will identify a candidate gene for detailed sequence analysis, or, 2) candidate genes will be excluded, eliminating some of the guesswork from future candidate gene approaches. In both instances, time and resources will be conserved.

## **MT08-004: Molecular basis of feline coronavirus pathogenesis and development of FIP in cats**

*Gary R. Whittaker; Cornell University. \$35,514*

Feline infectious peritonitis (FIP) is a lethal systemic infection in cats, caused by a feline coronavirus (FCoV). Infection by FCoV normally causes mild and often inapparent enteritis, in which case the virus is referred to as feline enteric coronavirus (FECV). In the "internal mutation" model of FIP, it is believed that a process of mutation within an individual cat confers the ability of FECV to infect macrophages, and so become feline infectious peritonitis virus (FIPV) - the virus that causes FIP. However, there has been little experimental support to date for the internal mutation theory of FIPV. This researcher has previously shown that the FCoV spike protein is differentially processed by host cell proteases, which leads to acquisition of a hyper-fusogenic spike protein and confers the ability of the virus to infect macrophages - and so initiate the process of FIP. This project will extend these studies to examine how differential cleavage impacts the

entry process of the virus in various cell types (epithelial cells, monocytes, macrophages and dendritic cells), and how this connects to usage of the different FCoV receptors (fAPN, Fc, DC-SIGN). The overall goal is to determine the molecular changes that account for the acquisition of an FIP phenotype by feline coronaviruses.

**MT08-007: Is the lack of oxalate degrading bacteria a risk factor for calcium oxalate urolith formation in cats**

*Jody P. Lulich; University of Minnesota. \$19,840*

Calcium oxalate (CaOx) is the most common urinary stone in cats. This disease is associated with dysuria, hematuria, and life-threatening urinary tract obstruction. Stone removal is the treatment of choice; however, many recur. A prerequisite for urolith formation is urine over-saturation with calcium and oxalate. Therefore, reducing urine concentrations of these stone components are essential to prevent reformation. Enteric colonization of oxalate degrading bacteria (ODB) is correlated with the absence of hyperoxaluria and/or CaOx formation in humans and rats. ODB can prevent enteric absorption of oxalate and increase the fecal excretion of endogenously produced oxalate, thus reducing oxalate levels in urine and preventing urolith formation. The role of oxalate degrading bacteria in cats with CaOx urolithiasis is unknown. We hypothesize that decreased colonization of the intestine with ODB is a risk factor for feline CaOx urolith recurrence. This study will determine the types and prevalence of ODB in the intestinal tract of cats with and without CaOx uroliths. It is expected that the prevalence of the ODB in the intestine of cats with CaOx will be lower than in clinically healthy cats. The results of this study will provide new insights into the pathogenesis and novel therapeutic targets such as probiotics for CaOx urolithiasis prevention in cats.

**MT08-009: Unraveling feline stone genetics: Searching for associations between polymorphisms in candidate genes and calcium oxalate stone formation in cats,**

*Richard E. Goldstein; Cornell University. \$23,615*

Urolithiasis is an extremely common feline disorder contributing considerably to morbidity and mortality of veterinary patients. Over 50% of all feline uroliths are calcium oxalate, including approximately 50% of cystic calculi and 75% of renal and ureteral calculi. Despite this fact, little is known about the genetic predispositions to form these calculi. Feline genomics is just now emerging with the publication of the 2X feline genome sequence, making genetic studies in cats more feasible than ever before. This proposal represents part of a broad initiative by the investigators to use a DNA bank from cats suffering from urolithiasis, which is currently being established, to unravel the genetic causes of and predispositions to stone formation in cats. Polymorphisms in four main genes have been associated with human calcium oxalate stone formation, presumably via increased calciuresis. The goal of this study is to evaluate those same genes in cats, to identify polymorphisms in the feline genes and to assess possible associations between the feline polymorphisms and calcium oxalate stone formation in cats. Finding such associations will contribute immensely to our understanding of feline urolithiasis pathophysiology, and will allow us to begin to unravel the genetics of feline stone formation. In addition, the findings of this study are likely to immediately enable the identification of groups of cats at increased risk for stone formation via genetic testing. Specific prevention programs can then be implemented for these cats, even prior to their first episode of urolithiasis.

**MT08-015: Heritable Progressive Retinal Atrophy in Persians,**

*Leslie A. Lyons; University of California, Davis. \$19,445*

Naturally occurring inherited retinal degeneration has been recognized in humans, cats and dogs. Retinitis pigmentosa (RP) is a heterogeneous group of heritable retinopathies causing blindness in humans. Progressive retinal atrophy (PRA) is the counterpart term in veterinary medicine. A complete and early-onset retinal degeneration with autosomal recessive inheritance has been described in Persian cats. Previous funding has supported the characterization of the inheritance, as well as clinical and histological features of this disease, and has genetically mapped the PRA-causing locus in cats to a specific chromosomal region. The backcross cat pedigree has been extended to 61 individuals for genetic mapping and disease characterization. Ophthalmic and neuro-ophthalmic examinations are performed on each animal on multiple occasions to determine disease status. A full genome-wide scan was performed on the backcross Persian PRA pedigree representing five generations. Feline-specific microsatellite markers were selected from feline linkage/RH maps with an average spacing of 10cM. Two-point linkage analysis was performed using the program LINKAGE. For fine mapping, additional markers within or flanking the critical regions were analyzed. This data suggested a critical region responsible for PRA is located at the short arm of a feline chromosome. However, poor coverage of the feline map prevents adequate comparison between humans, cats, and dogs in this region and does not clearly suggest a candidate gene. One hundred seventy-nine additional markers have been genotyped in the region, none of which have increased the likelihood of the gene identification. Thus, the overall genetic map of the region may be incorrect or since the significance values for the association are not increasing, a false region may have been identified and a further genome analysis needs to be performed. This project will continue to scan the proposed critical region to identify candidate gene mutation(s) within the region and also increase the marker coverage at other parts of the genome.